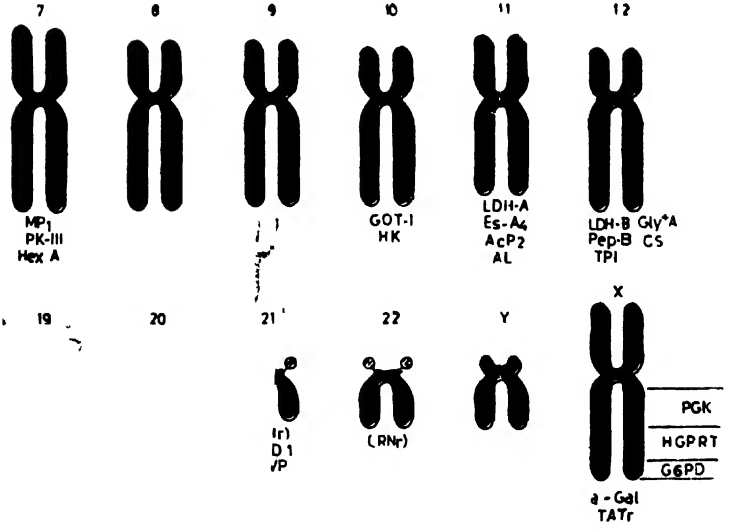
POPULAR SCIENCE

# GENETICS TODAY

JAGJIT SINGH

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# *Preface*

MODERN Genetics is a comparatively recent innovation. The reason is that we have hitherto been far more adept at understanding and manipulating the inanimate components of the universe around us than in controlling the living processes of plant growth and animal reproduction. This is natural. Physics and chemistry, the study of inanimate matter, are simpler and more uniform. Their growth and progress was a necessary prelude to providing the means of further advance in our understanding of the finer nuances of life processes. Indeed, both physics and chemistry had to reach a peak of sophistication attained only in the first few decades of the twentieth century before we could even begin to explain the incredibly complex mechanism of heredity and reproduction as well as the complicated sequences of reactions within the cells of the body, in the blood, lymph and elsewhere.

Even as recently as the turn of the century, the phenomenon of life remained quite inexplicable without recourse to a *deus ex machina* of some sort—God, spirit, purpose, entelechy, nisus, *elan vital* or some similar mystical principle. For until about seventy years ago, the complexities of the self-organisation of a single cell, not to speak of even the most primitive organism alive, were so enormous as to make any analysis of intercellular events all but hopeless. Since then the discovery of radioactive but stable isotopes of elements like carbon, phosphorus, nitrogen—the so-called tracer elements—whereby

chemical compounds passing into a cell may actually be labelled and recognised in subsequent metabolic products of the individual dose administered, has provided a new biological instrument of immense power. This along with the invention of electrically-driven ultracentrifuges which expose liquids to forces 100,000 as great as gravity, novel methods like electrophorsesis which sifts molecules with electric-forces, as well as new techniques much more delicate than those of light-microscopy such as X-ray diffraction and electron microscopy have enabled scientists to reveal the detailed structure of the ultimate building-blocks of cells, namely, atoms inorganic ions, water molecules, amino-acids, fats, sugars, proteins, nucleic acids and so on, giving rise to two new disciplines of biochemistry and biophysics.

With the emergence of biochemistry and biophysics, we are, now beginning to obtain increasing control and direction of those wonderful potencies we are wont to call "heredity" in somewhat the same way as we already do the great physical forces of nature. The new trend towards greater control of these latent "potencies" of life is already visible in the discovery of insulin, penicillin, streptomycin, cortisone and similar disease-curing chemicals which are not wholly synthetic but are elaborated by living things at the outset. As the mystery of the mechanism of "heredity" in virus, bacterium, plant, animal and man is unravelled more and more, many improvements in the cultivation of our basic food plants and breeding of domesticated animals have inevitably materialised. This is why if there is one single discipline of life sciences that is destined to mitigate and in some measure to repeal the primeval biblical curse pronounced on the labour of man—in the sweat of thy face shalt thou eat bread[1]—it is modern genetics, the science that is concerned with the inheritance of "superiority" in animals and plants and its exploitation for the benefit of man.

As Charles Darwin remarked in his Animals and Plants under Domestication, over a century ago, "hard cash paid down, over and over again, is an excellent test of inherited superiority". Since Darwin's day genetics has amply proved its

[1]Genesis 3.15

worth by showing that inherited "superiority" can be located, transmitted and availed of in the cultivation of plants and domestication of animals, the so-called cultigens of the commercial world. Cases in point are such celebrated cereals as hybrid corn, Mexican wheat and IR 20 rice, or famous breeds of cattle and sheep like polled (hornless) Herefords, Brangus, Marino, Rambouillet, Corriodale, etc. It is true that the genetics of cultigens is not the same as their production. It is a multidisciplinary activity involving many specialities like nutrition, plant physiology as well as pathology, endocrinology, chemistry of soils, water management, pesticides and fertilizers, etc. But genetics is the most important of them. It is the sole torch of light that the breeders and cultivators now have to guide their blind gropings. Even though there have been in the past many successful breeders who had little or no knowledge of genetics, practical breeders can no longer ignore the work of pioneer geneticists like Mendel and Morgan simply because they were engaged in what must have seemed at the time particularly inane exercises *a la Laputa* like growing peas in gardens and breeding fruit flies in bottles. And yet it is precisely these seemingly futile experiments that have yielded the basic laws of heredity. Based on their work modern genetics has evolved some pretty sophisticated techniques which are being used increasingly by present-day breeders as will be shown more fully in the text.

It is true that despite these advances, the production of better breeds of crops and animals is still a very slow process requiring prolonged and patient work extending over many years. But genetic theory does provide a more realistic basis for discriminating between fact and fantasy in assessing proposals for the improvement of agricultural production and animal husbandry. It seems to me that in this age of science fiction and "future shock" one must know the basic facts of life well enough not to be taken in by fantasies now being popularised under the rubric "genetic engineering". They are sometimes offered as short-cut solutions to difficult and interactable problem of producing sufficient food for the exploding population of our globe, or ridding the world of its present tensions by producing docile populations of human "clones"

by a feat of genetic "fix" seemingly taken straight from the pages of Aldous Huxley's novel, the Brave New world.

Similarly, modern genetics has shown that apart from the diseases, which arise due to environmental causes like outside infection and malnutrition, there is a class of diseases which are hereditary. Some of these diseases which like haemophilia used to be lethal long before the patient reached the reproductive age can now be cured or mitigated by expensive treatment. In others there is as yet no cure; but the treatment prolongs the agony by delaying the inevitable appointment with death. To the extent the patient with defective heredity is cured and enabled to reproduce, he transmits the defect to some or all of his progeny. Hence the paradox of our time; the more successful the treatment the more the incidence of disease the treatment is supposed to cure ! This is why the problem of treatment of hereditary diseases of certain kind has given rise to a severe dilemma among men of medicine as we shall see more fully in the text.

This book is an exposition of some of the great ideas of modern genetics to give the intelligent lay reader an understanding of its powers and limitations both in the production of cultigens and cure of hereditary diseases. It is only an explanation of some extremely basic concepts and principles of genetics that everyone ought to know if only for the reason that so long as two-thirds of world's population is undernourished and one-third actually sick and diseased genetics will remain the prima donna of life sciences.

**New Delhi** **Jagjit Singh**

# *Contents*

# CHAPTER I

## *What is Heredity?*

ALTHOUGH life's emergence from inanimate beginnings a few billion years ago is still a mystery, it is all but certain that the first forms of life were much simpler than any organisms that now inhabit the earth. The process by which these pre-Cambrian ancestral forms led to their myriad descendants of today is called organic evolution. Darwin was the first to demonstrate its occurrence in a convincing manner. In his "On The Origin of Species by Means of Natural Selection", he showed that animals and plants living today had not arisen by special creation of each species but by slow descent from very different onee in the past, some of which have left fossils. Nevertheless, despite a most thorough and objective analysis of data from all fields of biology to prove organic evolution through natural selection, his theory remained essentially negative. While his recourse to natural selection did account for the extinction of some forms and persistence of others by the "survival of the fittest", it could throw no light on the "arrival of the fittest". It could not possibly do so because the mechanism of heredity was not yet known. With his usual candour and honesty, Darwin admitted that "the whole subject of inheritance is wonderful" by which he meant to convey that the biology of his day

provided no clue to what continued for many years to be called the "riddle of heredity". Yet at the time Darwin made his remark (1868), the essential steps that led to unravelling of the riddle had already been taken by another great biologist, Gregor Mendel. He had shown the existence of those particles of heredity, he called "factors" and which we call genes, that enable organisms to reproduce themselves in their progeny.

Before Mendel all that we knew about heredity is epitomised in the old aphorism that "like begets like". That is, cats give birth to kittens that grow into cats and oak trees produce acorns that germinate into oaks. Likewise, human babies are always cast in human moulds and usually resemble in particular ways their parents and siblings a biologist's portmanteau word for brothers and sisters born of the same parents. Yet understanding why this is so, and how equally obvious variety within the family, race and species could arise and be preserved required more than mere recognition of the fact. It required a deeper probe into the processes of reproduction whereby living organisms maintain the continuity of life. Self-evident as these reproductive processes now seem to be, this self-evidence took long incoming. As a result of prolonged observations during the past three centuries, we now know that even though the process of reproduction occurs in different organisms in a bewildering variety of apparently quite distinct ways, these varieties belong basically to one or other of two main types. In the first type called *asexual* or *vegetative* reproduction, the body of the parent is divided into two or more parts and each part grows into a new individual. With animals this vegetative reproduction occurs chiefly among the simpler types, although some higher forms retain the ability to regenerate a whole body from a part. In some plants a small portion of the body, when removed and placed under favourable conditions, may establish itself as a new individual. For example, potatoes are cultivated more easily from pieces of tubers than from seeds and most fruit trees are propagated by cuttings or grafts. Far commoner, both among plants and animals, is the second kind known as *sexual reproduction* whereby a new individual arises from

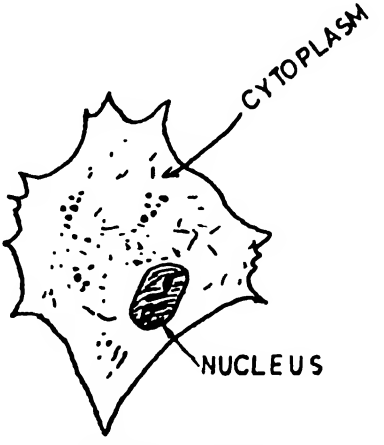
the fertilization of an egg which the mother produces by a sperm of the father.

Fertilization of the egg is a complicated biological process which could be understood only after the invention of the microscope. For even though the eggs of birds can be easily seen to be produced in the ovaries, the tiny vesicles on the surface of the ovaries in mammals are too small to be visible to the naked eye. They were, therefore, recognised as eggs only with the aid of the microscope. As a result of three centuries' observations made possible by increasing refinements of the microscope we now know that fertilization is merely the fusion of female egg and male sperm. Biologists have given both the sex cells, the egg and sperm, a common neutral name, gamete. Fertilization then is the fusion of two gametes, one from each parent, into a single cell called zygote. It is the zygote that grows during gestation into embryo, foetus and a new born infant. Such growth occurs by continued proliferation of a single cell into myriad others. Thus the fertilized human egg which at conception is a single cell becomes at birth an ensemble of billions of cells. It does so by successive division. The original parental or Adam cell, the zygote, divides into two cells, these two into four, the four resulting into eight, and so on until great numbers inevitable in such geometric progressions are produced. This process of multiplication of cells is known as *mitosis*, a biologist's technical term for what is plain cell division, whereby one cell yields two. For the most part the new cells formed at each division grow to the size of the parent cells before they in turn divide. Thus cell growth and cell division are ordinarily both involved in the development of an embryo from a fertilized egg.

But the subsequent growth of the embryo leads to the emergence of a variety of different organs like liver, lungs, eyes, bones, blood, muscles, cartilage, etc. This occurs because cells begin to "differentiate" changing drastically in shape and function. Thus lung tissues look different from bone, skin from blood, muscle from cartilage and so on because the microscopic cells that make up the tissues have evolved into entirely different forms. This evolution of cells

which are identical in early divisions into specialist cells in subsequent divisions, called "differentiation", is still one of the great unsolved mysteries in biology. But no matter how such differentiation of cells leading to the formation of diverse organs comes about, the fact remains that all the diverse o gans are ultimately made up of tissues such as bone, muscle, nerve, etc. which are all assemb'ages of cells. Since the cells which make tissues and organs are essentially all alike, a cell is to biology what an atom is to physics. While one is the basic unit of life, the other is that of inanimate matter. This is why the key to every biological problem including the riddle of heredity must finally be sought in the cell. It is, therefore, worth while, digressing a little on cell theory or cytology.

If we examine a cell under the microscope, we find that a typical cell consists of two parts—a central very dense nucleus and the surrounding less dense semi-fluid colloidal cytoplasm as shown in Fig. 1. The granular cytoplasm and its contents as




Cell with nucleus

FIG. 1

well as the denser nucleus are divided equally between two daughter cells in the process of cell division we earlier called mitosis. As a result the incipient daughter cells are just half the size of the parent cell. But this is a temporary phase. The

"daughters" soon grow back to full stature though this growth occurs in a series of complicated steps into which we need not go here. What is relevant to our present purpose is the fact that the living substance which carries heredity resides solely in the *nucleus* of the daughter cell at the end of each miotic division of its parent. The mechanism by which this nuclear genetic material is duplicated is remarkably accurate. It results in millions and billions of cells with exactly the same heredity or nuclear structure as the original. What then is this wondrous nuclear structure that is so accurately reproduced from cell to cell in each generation?

As a result of decades of observations and breeding experiments we now know that the nuclear material of the cell is organised in the form of minute rod-like or dot-like structures as shown in Fig. 2. These minute structures in thin tissue

A chromosome with dot-like thickenings which indicate the positions of genes

FIG 2

slices can be seen by staining them with certain dyes which they take up more readily than the rest of the cell. It is this property of becoming visible by means of dyes which gave them the name chromosome (chroma, colour, soma, body).

Chromosomes in turn are not homogeneous compositions nor single constituents. They are strings of those "particles" of heredity we earlier called genes, whose existence had been inferred from numerous breeding experiments like those of

Mendel. Such experiments had clearly shown that all heritable characteristics of organisms are transmitted unchanged without "dilution or blending" because they are carried by distinct indivisible particles of heredity Mendel called 'factors' and which we now call genes. Although genes have since been found to be actually very complex structures, being ultramicroscopic specks of nucleic acid which can reproduce themselves by copying, they are transmitted from parent to progeny as *indivisible* units of heredity so that they behave very much like atoms in chemistry. These "atoms" of heredity, the genes, are arranged in a very precise way in the nucleus of the cells of the organism. Literally hundreds or thousands of them are wrapped together linearly in microscopic packets we have called chromosomes. Thus if genes are atoms of heredity, chromosomes are its macromolecules. The study of heredity is therefore, the study of genes and chromosomes.

The number of chromosomes present in a cell nucleus depends on the animal and plant species to which the cell belongs. But in all cases they occur in pairs of similar or *homologous* chromosomes one contributed by each parent. The number (n) of chromosome *pairs* varies widely from species to species. It rises from 2 in a race of parasitic worms called *Ascaris megalocephala* through almost continuous gradations in numbers ranging from 3 in mosquito and 4 in banana fly to 10 in maize, 20 in mouse, 23 in man, 47 in goldfish up to 100 in the crayfish and even more in some ferns and protozoa. As already mentioned, each chromosome carries hundreds or thousands of genes. The human cell, for example, has been estimated to carry at least 40,000 genes, possibly twice as many. This number may seem large. But it is not so large when we consider the complexity of development activities that the genes have to monitor. For it is the genes that are responsible for all that is inborn and inherited in us. Thus, it is the type of genes we inherit that determines our sex, blood group, vision whether normal or colour blind, eye and skin colours, metabolic propensities, mental powers and a thousand other traits that make up our physical and mental personalities.

Such similarities between parent and progeny as that of eye

and skin colour or type of blood group are not the kind of stuff that can be packed in genes for onward "transmission". What is transmitted is a set of blue-print "instructions" that determine broadly the course of development and growth from conception to birth, then to adulthood, senility and death. These "instructions" are embodied in the genes and chromosomes in a code we have yet to decipher fully. But in principle it is analogous to the programme tape of a computer which carries the "instructions" for making it work in the desired way. Chromosomes and genes are thus in a manner of speaking microminiaturized "tapes" of heredity, the software of heredity that activates the computer hardware of environment.

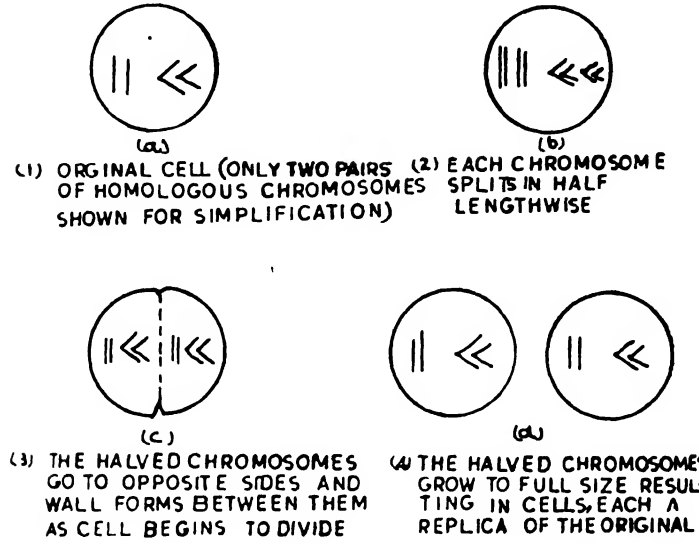
The computer analogy is not as far-fetched as it may seem at first sight For the celebrated logician, A.M. Turing proved in 1936 that one can *in theory* make a computer—it is now called a universal Turing machine—which can reproduce itse f by reading its *own* description from a tape. Now such a description may be recorded not merely on a paper tape but also in the genetic material of which chromosomes and genes are made. It is now known that compounds of carbon by chemical bonding, isomerization (both structural and stereo), multiplication of benezene ring structure polymerization, etc. provide infinite variety of materials which can and do carry genetic information of great specificity given them at birth in coded form in the cell. The *hi fi* reproduction of chromosomes in the nucleus of the daughter cell when a parent cell divides into two is verily a marvel of microminiaturization. Indeed, in that infinitesimal speck of organised nucleic acid that is the nucleus of the human zygote, the fertilized ovum, there is packed complete information to create the whole man. We shall dwell more fully on the nature of this information in chapter V. It will meanwhile suffice to say that the self-same information is duplicated in the nucleus of every daughter cell to which it gives rise not only during gestation when the zygote grows into embryo through foetus to new born infant but also throughout the infant's subsequent life. The 46 chromosomes in each somatic or body cell contain the same information as was in the initial zygote. It, therefore, follows that if we could provide the right conditions for its development

*any* cell in the body could grow into a complete human being, an identical twin, as it were, of the person who provided the the somatic cell.

The possibility of duplicating a human being by taking a single cell from the skin of a person's hand and making it grow asexually into a whole man is as yet only theoretical and we shall revert to it in the next chapter. But in plants it has actually been accomplished. As is well known, ordinary plants are grown by sowing seeds. The seed is the equivalent of the zygote, the fertilized egg, so that, when planted in the earth, its natural womb, it begins to sprout in course of time into a full grown plant. But during the early 1960's Professor F.C. Steward devised a novel way of growing garden carrot plant. He used differentiated cells instead of seeds, yet amazingly these cells from carrot root when exposed to various nutritive media began to proliferate. Eventually, with patience and changing media and techniques, Steward managed to coax the individual root cells to form clumps, and organized masses. More importantly, they began to differentiate again into other kinds of cells. He finally succeeded in carrying one individual cell to the ultimate stage of a complete carrot plant roots, stalk, leaves, flowers, seeds and all. His experiments apparently show that any plant cell may be made to grow *asexually* into a full plant, provided an appropriate technology is applied.

Plants, however, are not animals. Nevertheless, the analogous idea of growing a whole animal from one somatic cell *asexually* has been mooted on the ground that what is possible with a plant cell should, at least theoretically, be equally possible with an animal somatic cell as well. For animal somatic cell has all the genetic information required to reproduce itself, as may be readily inferred from our knowledge of the mechanism of cell division. We know that before a cell divides, each chromosome in its nucleus somehow makes another duplicate just like itself with the same genes in the same order exactly like a miniature Turing machine that can reproduce itself by reading the description of its own makeup. Having in this way duplicated themselves, the old chromosomes separate from their newly-formed duplicates when the parent cell divides subsequently in two. Both daughter

cells thus receive exactly the same numbers and types of chromosomes and genes as the parent has (see Fig. 3.)

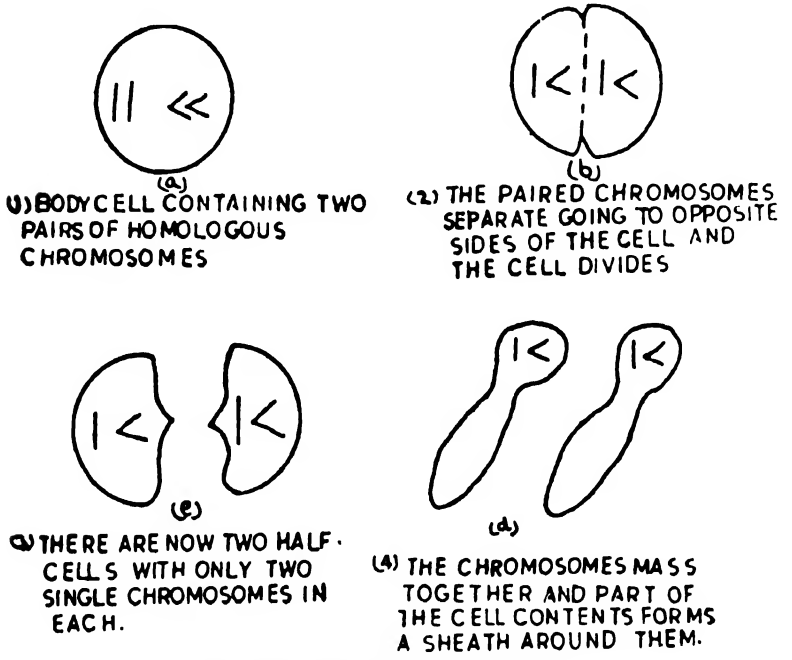



How a fertilized egg multiplies by mitosis

FIG. 3

Now if each "daughter" cell in its nucleus has as many chromosomes as the parent, the fusion of any two ordinary body or somatic cells would give rise to a zygote with twice the usual number of nuclear chromosomes. Consequently the nucleus would be doubled in size in each generation. Obviously such geometric doubling of the number of nuclear chromosomes in each generation cannot go on very long. In fact, it does not occur at all because as already noted, the cells of individuals of any one species are all found to contain exactly the same number of chromosomes in each generation. It therefore, follows that it is *not* ordinary body cells that are concerned with reproduction. At some stage the nucleus of the ordinary cell must be *halved* to produce another kind of cells, the sex cells, which play the key role in reproductive process. These sex cells are the gametes—the sperm and egg—whose union gives rise to the starting zygote.

The gametes as also their plant counterparts, the spores, are therefore, formed by yet another process of cell *reduction* whereby the number of chromosomes in the nucleus of the body cell is reduced by the required half. The process of halving the nuclear chromosomes is known as *meiosis*, a Greek word meaning reduction, (see Fig. 4). While mitosis




How gametes are formed by meosis

FIG. 4

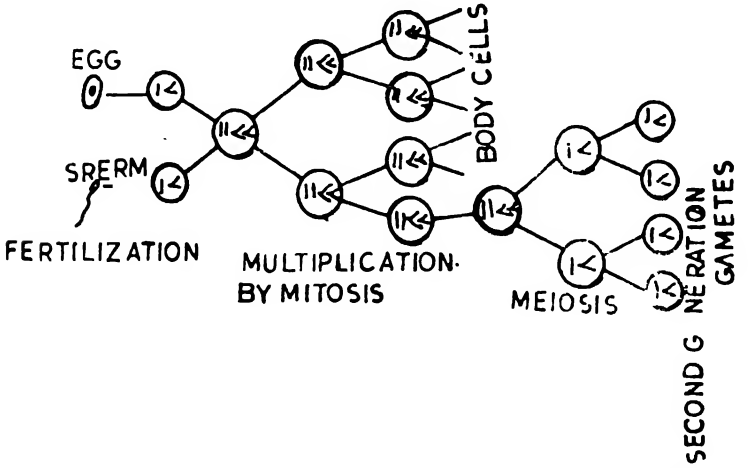
conserves the integrity of the nuclear genetic material when the body cell proliferates by successive divisions, meiosis reduces it by half as a prelude to gemetogenesis so that when two gametes fuse to form one zygote, it has the same genetic composition as its parent. Had the process of cell reduction (meiosis) whereby gametes are produced been known in Shakespeare's time, he might have enumerated nine ages instead of seven in the famous passage commencing with the line, 'All the world is a stage' :

*At first the divided gamete,*
*Half in ovum and half in sperm.*
*And then the United Zygote*
*Gestating in his mother's womb.*

It is in virtue of meiosis that the gametes have precisely *half* the number of chromosomes in the body cell. And it is because of mitosis that the body cell retains intact its genetic patrimony in all the successors it breeds by division. Consequently both the basic processes of cell division (mitosis) and cell reduction (meiosis) are fundamental in almost all biological reproductions. The means by which they occur are the most elaborate, and yet in principle the most uniform, pieces of organisation so far discovered by the microscope. For we see them carried out in most plants and almost all animals in the same series of steps with the same beautiful sychronizations, and succession. The celebrated British cytologist, Sir C.D. Darlington, who first observed these synchronizations was so enchanted by their harmony that he called mitosis a "symphony consisting of four movements— beginning, two middles, and an end." He might as well have added that if mitosis is a symphony, meiosis is both the melodic overture as well as finale of the orchestra of biological inheritance. It is by keeping both in double harness that life has driven itself from its primitive pre-Cambrian origins to its present peak of sophistication and complexity. It is, therefore, no mere accident that we see them at work in almost all organisms be they the lowly banana fly, the favourite "guinea pig" of the experimental geneticists, or, the geneticist himself, the acme of biological evolution.

In the banana fly, for example, the normal somatic or zygotic number of chromosomes in the nucleus is eight arranged in four pairs of similar (homologous) chromosomes. But when these somatic cells give rise to sex cells or gametes by meiosis, each gamete contains only four chromosomes one of each pair of four in the somatic cell. Likewise, in man, the zygotic number is 46 and gametic number is 23. We thus observe that cells in most organisms are of two kinds the ordinary somatic cells that make up the main bulk of the body and

the special sex cells, the gametes, that are derived from the somatic cells by *meiosis* for purposes of reproduction. The former contain two sets of chromosomes and are, therefore, called *diploid.* The latter contain only one set of chromosomes and are known as *haploid.*




Haploid sex cells and diploid body cells reproduce each other as shown in this Figure which is merely a juxtaposition of Figs. 3 and 4 illustrating respectively the two processes of cell *Division* (Mitosis) and cell *Reduction* (Meiosis). The chief merit of the juxtaposition is the demonstration of double nature of the body or somatic cells and the simplex cond tion of the sex cells or gametes

FIG. 5

Since chromosomes are the sole repository of biological inheritance, haploid gametes with only half the chromosomes of the diploid somatic cells contain only half the genetic information to create the organism. The human sperm and ovum, for instance, each has information to make half a man. But even though both sperm and ovum have equal information, there is a curious contrast between the male and female sex cells in any mammal including man. Male sex cells, the sperms, are extremely small—barely visible under a powerful microscope—and are produced in astronomically large numbers—300 million in a single ejaculation. The ova, on the

other hand, are much bigger and are produced much more parsimoniously than the sperms. They are laid down before birth to provide the few hundred needed for one to mature and be liberated each month from the menarche to the menopause. The mature ovum which is a large cell many thousands of times bigger than the sperm contains a large supply of nucleic acid building blocks and other nutrients to allow of all the activities which will follow fertilization. Because of these contrasting features of their size and scale of production, as well as the need to carry the fertilized zygote in the female womb during gestation, it is the male sperm that has emerged as the main tool for furthering the great biological revolution of our time designed to delink sex and reproduction. Such delinking has already occurred in the current vogue of artificial insemination that has revolutionised cattle breeding. As is well known, artificial insemination has become virtually standard practice in dairy cattle breeding in the last thirty years or so. An elaborate technology has been developed so that a bull with the natural capacity to serve 30 to 50 cows annually can now father more than 2000 calves. Semen appropriately diluted in saline solution containing glycerol and frozen to temperature of dry ice—70°C, can keep bull spermatozoa in viable form for at least four years. It can therefore be distributed for use far and wide.

Recent research has overcome the handicap of the female sex cells in that they are produced singly in each ovulation cycle instead of millions of sperms per ejaculation to yield a procedure parallel to artificial insemination. For means have now been evolved to stimulate within the female multiple release of mature eggs with the aid of a pituitary harmone. These eggs can be collected, fertilized, and transplanted to genetically less endowed foster mothers. It thus permits the multiple distribution of eggs of a highly selected female into diverse recipient females thereby enabling it also to transmit its *mouie* of genes to hundreds of offspring. Possibly, too, techniques involving mature eggs could be combined with deep freezing to allow indefinitely prolonged storage.

Now the modern objective in breeding cattle is to increase the total yield of milk and butter fat for each lactation period.

All other requirements are secondary. The criterion for a bull's or cow's work is, therefore, simply arrived. If he or she can regularly produce daughters with a better record of milk yield than their dames or (sires), his (or her) services will be in great demand. Such proof of his work may take several years. But once produced it is indebatable. No such clear criterion of human excellence can be specified. Consequently when we attempt to dissociate sex from reproduction in the case of man, as we may well have to do, to counter the global population explosion, we hurtle against a two-fold difficulty. First, how to let people enjoy sex without reproduction. Second, if human reproduction is to be entirely divorced from sex and strictly licensed, who should be licensed to reproduce? The former is the vexed problem of birth control. We shall skirt round it to come to the latter which is more relevant to our present theme. For some enthusiastic geneticists have seized on the potentialities of human artificial insemination to dream of breeding supermen of the future. The celebrated American geneticist, H.J. Muller, for example, suggested a few years ago, that the possibility of using the semen of outstanding men for artificial insemination should be considered. If he could have devised an indubitable criterion of human worth as cattle breeders have done for selecting the prize stud bull, there might well be justification of sorts for not only using the proved individual as a donor for artificial insemination, but also for storing ampoules of his semen in liquid nitrogen to be used with suitable recipients in future generations. But no such criterion of human genetical excellence can be devised, simply because we might dispute endlessly about the meaning of the word "excellence" in this context. Moreover, even if we resolved the dispute by circumscribing its scope to some particular field of human endeavour and did agree on what is "excellence", there is no knowing that it would be passed on to children. It is true that there have been some famous families reputed for excellence in music, architecture, and mathematics like the fifty seven Bachs, who were musicians, the thirteen Watts who were architects and the eight Bernoullis who were mathematicians. But for every Bach and Bernoulli we may cite, there are

thousands of gifted men who failed to transmit their intelligence to their progeny. And even in the case of those who seemed to do so, who can say which played the greater role in the transmission—heredity or the home and educational environment as we shall see more fully in the next chapter.

# CHAPTER

# *Heredity and Environment*

AS we have seen, no matter whether an organism reproduces sexually or otherwise, it starts life as a small bit of parental body such as a seed, graft, cutting, or, fertilized egg. It is this bit of parental body that grows to enormous size to make the offspring. The body of an adult man, for instance, is fifty billion times as massive as the fertilized egg from which it orginated. The source of such an enormous increase in mass is evidently the food that the organism continually extracts from the external environment for its own buildup. This is true of all organisms whether men, mice, cats, or green plants. Every organism consists quite literally of transformed food.

The transformation of food and nutrients in the environment into the live stuff of which the body of the organism in question is made, is the outcome of thousands of intricately interwoven developmental processes. The complex of such delicately balanced processes is compendiously called metabolism. Every organism has its own characteristic form of metabolism whereby it responds during the course of its development to the components of its external environment such as food, nutrients, water, air, heat, light, etc., in its own peculiar way. Although metabolic patterns are different in different organisms, the goal of every metabolism is essentially

the same, namely, to enable the organism to assimilate the materials in its environment to become a more or less faithful copy of its parents and other ancestors. That it becomes a faithful copy is due solely to the genes and chromosomes it inherits in the originating "bit" of parental body. But the qualifying "more or less" is a consequence of the environment in which the initial "bit" grows. Thus while the genes inherited in the parental "bit" ensure the recurrence of like forms of metabolism in the progeny, the ambient environment in which the "bit" grows determines the way the inherited metabolism actually manifests itself. This is why both heredity and environment go hand in hand in shaping the life of the offspring from cradle to grave. Indeed, so indissoluble is the bond between the two that life very often advances itself by overcoming the obstacles of its unfavourable environment by making a piece of its own suited to itself and carrying it about with it. This is how our acqueous ancestors ventured out of their marine habitats to live on land as reptiles, birds, mammals and primates. Our own *milieu interne*, the salt content of our blood stream, carries the imprint of its origin in the seas. What biological evolution aeons did ago we are beginning to do now when we decide to land man on the hostile planetary worlds in our solar system like the moon. A modern astronaut in a lunar voyage carries with him a prefabricated miniature of his terrestrial environment, his capsule and space suit. It is, therefore, obvious that consideration of life without its environmental support is all but meaningless. All life is the outcome of a complicated interaction between heredity and environment.

However, even though both heredity and environment determine the characterstics of the offspring, different characteristics in the offspring do differ widely in the degree to which they are dependent on hereditary genes and the prevailing environment. At one extreme there are traits which wholly depend on the genes the organism carries regardleses of the environment so long as it is at all compatible with survival and growth. A case in point is varieties of peas which may either be wrinkled or round. Whether a pea will be wrinkled or round is purely a gene effect. Likewise, whether a man will

be blood group A or B, whether a cow will be horned or hornless, and whether a mouse will be grey or white, depends wholly on the genes it carries no matter what the environment. On the other hand, there are cases where even individuals having identical genes may develop differently in different environments.

Such persons as inherit identical genes are called identical twins in contradistinction to fraternal twins. Fraternal twins do not have the same heredity as they arise from the fertilization of two ova by two sperms at the same time. They may, therefore, be of the same sex as the bibilical twins Eeau and Jacob or of opposite sexes like Appollo and Artemis of Greek mythology. In general, they are as different genetically as ordinary brothers and sisters. Identical twins, on the other hand, arise when a single fertilized egg splits into two, and each half develops into a whole embryo (See Fig. 6). They are, so to speak two halves of what nature originally meant to be one person. But as all the cells of one person carry the same genes, identical twins are genetically as alike as congruent triangles. But even though genetically congruent they may develop differently in subsequent life. Thus one of the identical twins may contract syphilis and become blind or insane or both, while the other may remain normal. The difference in development in such cases is entirely environmental.

Between the two extremes where the trait appearance is either wholly genetical or wholly environmental, there are many others which are a betwixt and between of heredity and environment. Thus freckling is a gene effect which requires sunlight for its appearance. Only a person with the appropriate gene will develop freckles. But whether or not he will do so, and whether he will be lightly or heavily freckled, depends on the extent to which he is exposed to sunlight during the course of his life. Two identical twins having freckling genes will develop different patterns of freckles if one of them leads an outdoor life and the other indoor. The former will be much more heavily freckled while the latter will hardly have any. Similarly, even though wrinkled peas owe their wrinkles wholly to the genes they inherit, no two peas have the same pattern of wrinkles simply because no two peas, not even in the same

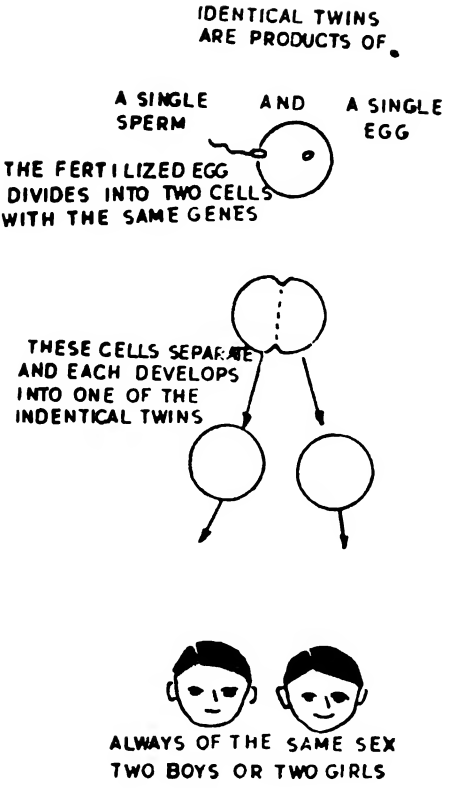
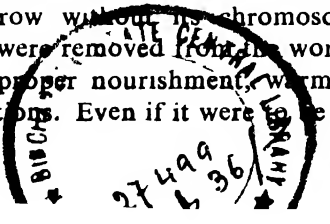



Fig. 6

pod grow up under exactly the same conditions. Or again to cite another instance, dwarfism is a gene effect. Individuals inheriting such a gene fail to achieve normal size under the same conditions which permit normal growth in related individuals with an alternative gene for growth. Nevertheless, an overfed genetical dwarf may grow bigger and fatter than a starved sibling with normal genes.

From the foregoing illustrations it is obvious that the constellation of traits that an offspring will exhibit depends on a complicated course of development in which the trait-sponsoring genes in its genetical mould interact with an environment.

Such interaction may be more obvious in some cases than in others but it indubitably exists in all. Thus we may be reasonably sure that a blue-eyed person owes his eye colour to the inheritance of genes for blue eyes. But had he inherited the genes for some mental trait, say, mathematical ability, there is no guarantee that it would always show up. We would have to consider the special environment in which the person develops, because anyone, even though he had the right heredity, might appear very stupid at mathematics. if he had the wrong training. One such near miss was the mathematical prodigy Ramanujan, who might well have died, 'mute and inglorious' had he not been rescued from dire poverty and trained by his mentor, the Cambridge mathematician, G.H. Hardy. But because a potential mathematical genius might fail to blossom while blue eyes almost always arise, there is no reason to conclude that blue eye colour is entirely a matter of heredity and mathematical ability entirely a consequence of environment. Each trait requires both heredity and environment for its development. It happens. however, that the normal environment supplies all the conditions necessary for blue eyes, possibly because this trait develops in large measure, while the embryo is in the uterus of the mother, where the relatively few conditions required for its emergence do invariably arise. The conditions that lead to the emergence of a mental trait are, on the other hand, extremely numerous as well as remote. They come into play during the entire life of an individual and appear in the most diversified forms in his environment. It is thus obvious that heredity is to environment what programme is to computer hardware. Both the programme and computer hardware are required to make the computer tick. Either is helpless without the other. This is why the question, which is more important, heredity or environment, is a pseudo problem. It has no answer. For obviously both are absolutely nececsary and neither can be said to be more important than the other. The fertilized egg could not grow without its chromosomes; neither could it develop if it were removed from the womb of the mother and deprived of proper nourishment, warmth, and other environmental conditions. Even if it were to be transferred to a test

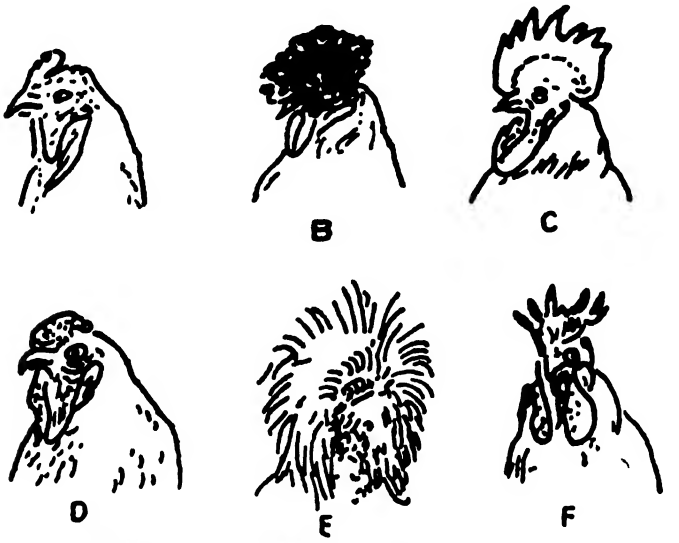


tube, the test tube would have to duplicate the environment of its mother's womb in order to ensure the survival of the embryo. In short, the fertilized egg develops into a new organism because of the action of the genes and chromosomes it inherits from its parents on the ambient environment.

The inherited gene complex or genetical mould of an organism is called its genotype. It is determined by the number, type and arrangement of genes in the originating fertilised egg or seed. The trait actually exhibited by the offspring or its outward appearance is cal'ed phenotype. The phenotype includes all observable traits whether anatomical, physiological, psychological, mental or whatever. The phenotype of an organism is, therefore, the consequence of the growth and development of a genotype in a certain environment. Since neither the phenotype, the actual appearance of an organism, nor the environment remains constant, it is more true to say that its phenotype at any given moment is determined not only by the environment that prevails at that particular moment but also by the whole succession of earlier environments it has experienced during its life time. Every plant, animal or person is the outcome of its genotype and its life experiences.

Now if the final form of an organism, its phenotype, is the result of a complicated interaction of its inherited genes and the environment in which it has lived from the moment of its conception, we must somehow segregate the influence of genotype and environment in order to produce improved genotypic variants of cultigens which when raised under farm conditions give greater yields of grain, fibre, milk, meat, eggs, wool and other products useful to man. But the segregation of such a tangled interaction as that of heredity and environment is no simple matter. It requires recourse to a series of replicated experiments performed according to procedures expressly designed to assess the relative influence of genotypic and environmental factors. The formulation of such procedures has now become a fairly complex discipline by itself. It is called the Design of Experiments. We will not dwell on it except to remark that the procedures designed essentially consist in growing plants in adjacent plots or breeding animals in contiguous cages and pens under controlled conditions so

as to reduce the inevitable environmental disturbances to the barest minimum. It can then be said that phenotypic differences between individuals that are reared in similar environments can as a rule be attributed to differences in genotypes. Thus the differences in varieties of poultries shown in Fig. 7 are mainly genotypic, since they appear in individuals reared under similar conditions.




Variation in the head appendages of male fowls:
Each form is typical of a breed varietv.

Fig. 7

Broadly speaking, genetical experiments designed to disentangle the effects of genotype and environment must fulfil two basic conditions. First, the animals and plants should be raised under similar conditions or under conditions that differ in known ways. Second, it is necessary to have a supply of individuals with similar genotypes, or with genotypes differiny in known ways. Although neither of these conditions can be fully satisfied in practice, it is relatively easier to make the environment reasonably uniform by raising experimental animals or plants in incubators or in constant-temperaturt rooms in uniform soil by treating them alike. The uniformity

thus secured is never absolute as some marginal environmental diversity unavoidably creeps in.

The fulfilment of the second condition, namely, control of genotypic variation, becomes progressively more and more difficult as the complexity of the organism increases. It occurs automatically in the case of simple unicellular organisms like bacteria which multiply by ordinary cell division—one cell growing into two and two into four and so on. This is why colonies of bacteria of identical genotype are obtained by isolating single bacterial cells and permitting them to grow and divide on suitable nutrient. Such colonies are called clones. Cloning is merely the production of genetically identical copies of an individual organism. It is also easily secured in the case of some simpler plant organisms that reproduce themselves asexually by simple fission, or by buds, runners, stolons, etc. For example, one may take several cuttings from a specific plant (indeed, the term klon is the Greek word for "twig" or 'slip") each of which can then develop into a mature plant—genetic replicas of the parent. Some varieties of fruit trees like oranges are clones propagated for many generations by grafting buds of a single original tree. Another instance of a clone is Steward's asexual reproduction of garden carrot (which is normally produced sexually) from a single (somatic) cell of a parent plant mentioned in the last chapter. But the complex technology employed by Steward to produce it is only an index of the difficulty in producing clones of more complex organisms like higher plants and animals. In fact, cloning of higher animals including man is as yet only a theoretical, if remote, possibility. It derives its credibility from a laboratory procedure that seems to provide a viable alternative to sexual reproduction. For when an egg cell is stimulated mechanically or chemically, it will start the division process which leads to the adult form even though it is unfertilised. This virgin birth, or parthenogenesis, occurs in nature, the typical example being the honey bee, whose fertilised eggs produce workers and queens and whose unfertilised eggs develop parthenogenetically into drones or males. Beginning with simple sea forms, laboratory parthenogenesis progressed up the evolutionary ladder to the point that in 1939 a whole rabbit was reported

created from an unfertilized egg. However, since in most species the unfertilized sex cell, unlike all of the other cells of the body, is haploid, the individual formed is not genetically identical to its mother, or indeed genetically identical to anything.

To produce a genetical replica of an animal, it is, therefore, necessary to devise a technique complimentary to that of Steward's asexual production of carrots from a single cell. Such a technique was invented by Professor John Gurdon. He exposed a frog's egg to radiation so deftly as to destroy its nucleus without damaging its body. He then managed, by equally complicated mechanisms, to take the nucleus from an ordinary body cell of the frog (with its full complement of chromosomes) and intrude it into the egg cell. So far, it was only an assumption that the nuclei of all cells, regardless of how different they might be, were identical in their genetic inheritance and contained the entire information for reproduction of a differentiated, multicelled adult. But Gurdon's production of the whole frog from his newly constructed egg cell, which was now the equivalent of a fertilized egg, is the first ocular demonstration of what was hitherto only an inference. The frogs he produced were perfectly normal frogs genetically identical to the frog that donated the nucleus.

Although John Gurdon used an intestinal cell, he would have obtained the same results had he used any other body cell which could have been that of a male or a female. The enucleated egg into which the nucleus was injected was also unimportant, genetically speaking; it was merely the environment. Gurdon thus showed the way to produce thousands of genetically identical offsprings in the laboratory at least in frogs.

But cloning of frogs is not the same thing as cloning of higher animals like dairy cows or human beings. Bovine and human ova are vastly different from frog ova. Contrary to what one might expect, the frog egg is huge compared to the microscopic human ovum. The reason is obvious. The frog egg is like a chicken egg in that it must carry all the nutrient to support the complete development of the embryo. In the human being, on the other hand, the egg is implanted in the

wall of the maternal uterus soon after fertilization and a placenta forms which permits direct feeding of the foetus by the mother. The size of human ova, therefore, is incredibly small considering the size of the offspring. H.J. Muller once calculated that all the human eggs from the total population of the earth (then two-and-a-half billion) would occupy less than a gallon of space. Because of the minute size of human and bovine ova, further advances in microsurgery and laboratory techniques will be necessary before cloning of higher animals like cattle and man becomes possible. Although a book that became an instant best-seller was written by an unscrupulous journalist professing to describe an actual example of human cloning, it is now well known that the book was a fraud. It was a case of pure science fantasy masquerading as a scientific fact. No cloning of even any mammal let alone a human being has yet taken place.

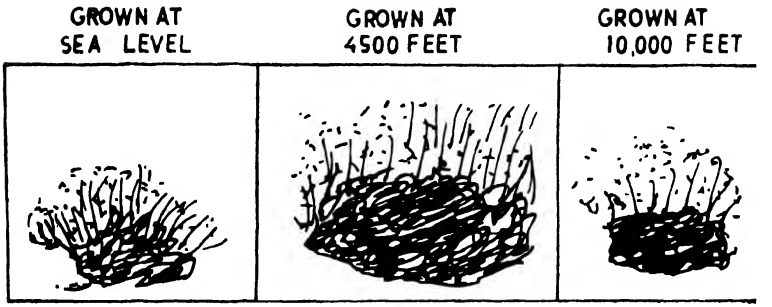
Since cloning of higher animals is still not possible, all that can be done is to control their genotypic variation by other means. Even this is a difficult task, the magnitude of the difficulty to be surmounted depending on the nature of the organism. The least difficult are organisms that reproduce themselves by self-fertilization or 'selfing' for short. Such organisms breed progeny by fertilization of female gametes by male gametes both of which are produced by the same individual. They are hermaphrodites[1] in which the same body carries organs of both sexes.

Hermaphroditism is a common condition in many groups of plants and in some animals. Most cultivated wheats, oats, barleys, beans, peas, etc. reproduce chiefly by self-fertilisation. Some animals like fresh-water snails also reproduce in the same way The progeny of a single individual obtained by selfing is called a *pure line*. Members of a pure line do not necessarily have identical genotypes but the genotypic uniformity among them is likely to be much greater than in progeny by cross-fertilization of different individuals.

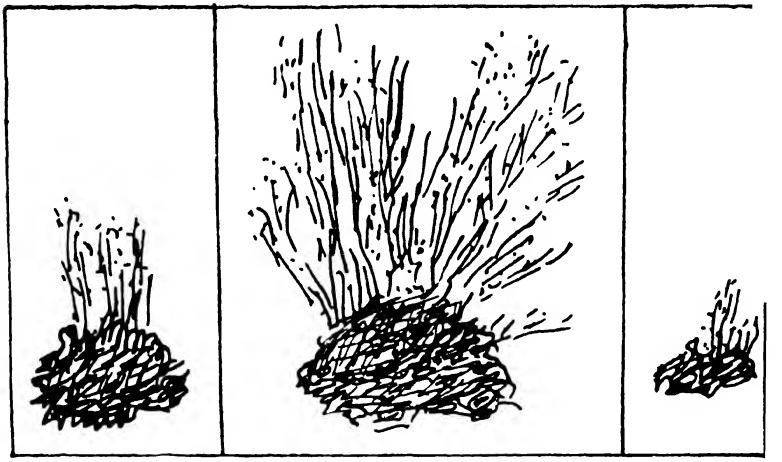
[1]Derived from Hermaphroditus, mythological son of Hermes and Aphrodite who became joined in body with the nymph Salmacis, the united body retaining the characteristics of each sex.

Genotypic variation is most difficult to control in organisms that reproduce sexually by the fertilization of the female egg by the male sperm. For reasons explained in chapter VI the number of possible genotypes that can be produced by mating even a single parental couple is so enormous that the question of obtaining either clones or pure lines in the case of sexually reproducing organisms cannot arise. All that can be done to minimise genotypic variation is to resort to inbreeding, that is, to mating of close relatives such as brothers and sisters. After some generations of inbreeding, we obtain *inbred lines* which show greater genotypic uniformity than in the initial crossbred population. Inbred lines are of great importance both in scientific experiments and agricultural practice. One can measure the influence of environmental factors, such as amount and kind of fertilizer and type of soil in crop plants by growing members inbred of lines under different conditions. In laboratory animals such as mice, rats, guinea pigs, the existence of inbred lines is useful for the measurement of effects of nutrition, sensitivity to disease, effects of drugs, etc. We shall revert to the question of inbreeding and pure lines in chapter IX.

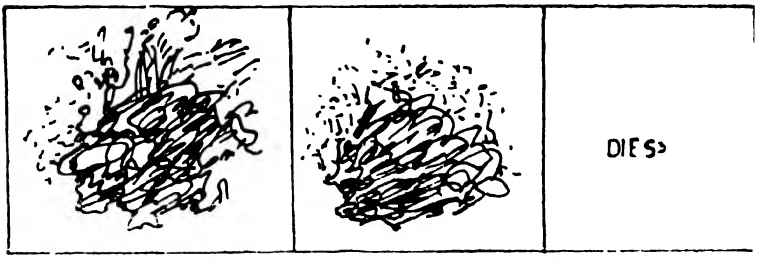
Having devised ways of controlling environmental and genotypic variations, one may breed individuals of uniform genotype under different environmental conditions or vice versa. Consider, for example, the growth of three different races of a plant which grow wild in different habitats, especially at different elevations in mountains as shown in Fig. 8. The differences among plants in the same vertical column are obviously genotypic and are due to adaptation of their ancestors to different altitudes. On the other hand, the differences in plants in the same horizontal row represent responses of the same genotype to different environments. Now the plants in each horizontal row are members of a clone having been obtained by dividing a single individual and replanting the parts in different places. It follows that these plants are genotypically alike or very similar. And yet it can be seen that these plants with uniform heredity look very different when grown in different environments. The same genotype reacts to different environments in different ways,




ALPINE RACE FROM 10,000 FEET



MID ALTITUDE RACE FROM 4,500 FEET




COASTAL RACE FROM 600 FEET

Fig. 8

so that the plants develop differently and acquire different phenotypes. The small size of the plant on the right in the middle row in Fig. 8 is simply a different response of the same genotype which in another environment reacts to produce the tall and strong plant in the middle of the same row.

The diverse phenotypes that may arise from the interplay between a given genotype and various environments in which this genotype may live constitute the *norm* or *range* of reaction of that genotype. Since the environmental diversity to which a genotype may be exposed is practically infinite, we can never know the entire norm of reaction of any genotype. Nevertheless, it is very important to know, particularly in man and cultigens, how a given genotype will respond to certain environments which may exist naturally or be specially contrived. It is by comparing the norms of reaction of given genotypes to specific environments that great improvements in the production of cultigens have been accrued. It is in this way that we have found that the precise ration fed to a steer, a cow, or a laying hen makes a great deal of difference in the number of pounds of beef, quarts of milk, or dozens of eggs produced. So powerful may be the effects of environment on characters of this sort that much attention is given in agricultural practice to manipulation of factors such as feed, fertilizers, water, temperature, time of planting, etc. in order to obtain the most desirable phenotype from the norm of reaction of a given genotype.

The problem of the practical breeder of cultigens is, therefore, two-fold: (a) given the genotype, discovering the precise constellation of environmental conditions yielding optimal quality phenotype, and its converse, (b) given the environment discovering the ideal genotype to match it as perfectly as possible. While great progress has, no doubt, been made in solving (a) with regard to a great diversity of commercial crops, farm animals and bacteria that ferment our wines and antibiotics, the search for ideal genotypes suited to certain unmanipulable constraints of environment like arid regions we may wish to bring under cultivation is still largely a hit-and-miss affair. The reason is that most of the characters of an animal or plant which are economically useful such as

milk yield, litter size, egg production, crop weight, etc. depend on a large number of genetic and environmental factors. Because of the enormous complexity of this interaction it is often impossible to discriminate between genetically and environmentally based effects. Neither is it possible to know what combinations of genes produce most phenotypic differences in populations of cattle and plants especially when they concern traits of economic value to man. Nor could we just say what the effects of given genes in untried combinations would be. In all practical applications of genetics it is, therefore, well to emphasise the principle of non-congruence of genotype. Which is merely to say that we cannot yet identify the genes that produce particular traits we desire most. One has still to rely on the empirical methods developed by plant and animal breeders which assess an individual's genetic potentialities by the study of his progeny or other relatives rather than by gene identification which is seldom feasible.

# CHAPTER III

# *Mendel's Laws*

WHEN Mendel began his celebrated breeding experiments to delve into the riddle of heredity, he found the experimental oracle he invoked as silent as the Sphinx. Thus his breeding of mice and bees which he carried on for years on end led him nowhere. Following the golden rule that whereof one cannot speak thereof one must remain silent, he published nothing about his work on them. He might have drawn an equal blank from his experiments with ordinary garden peas. But he had the serendipity to ignore experimental results that produced peas showing "irregular and inconstant variation". The irregular ones made 'noise' that disturbed the 'signal' he wished to infer from his experiments. For they seemed to vitiate the verification of a bold piece of abstract thinking he had ventured to conceive.

Steering himself clear of the earlier notions of heredity that fertilizing materials were "fluids" or "essences" that somehow got mixed in biological reproduction, Mendel thought of heredity as "particulate" in that it was transmitted in discrete units he called "factors" and we now call genes. Mendel's genius lay in formulating a new theoretical model of biological inheritance in precise terms and then testing it by simple direct experiments. The model simplified a vastly complicated situation without oversimplifying it. It made the experimental

oracle speak in a lingo one could understand. The reason why the oracle remained silent or rather spoke in an unintelligible babel of tongues for so long, lies in the fact that no complicated phenomenon like heredity, or, for that matter even a simple one like the motion of material bodies, can be understood by merely observing things as they happen around us. Experimental observations made without the "right" supporting theoretical framework are usually sterile. Thus falling bodies had been observed for millennia without revealing the fundamental laws of motion. They were only discovered when Galileo broke away from the earlier theories of Aristotle and postulated that force is not required to sustain uniform motion but only accelerated motion. He was then able to verify his theory by suitably designed experiments such as dropping bodies from top of the Leaning Tower of Pisa or rolling stones down inclined planes. Observations have, therefore, to be carefully designed even in the simplest cases to confirm or deny some preconceived conceptual framework or theory that is to explain the phenomenon in question. This may contradict the usual belief that scientists discover truth by remaining sternly objective in making their observations which then lead them to the right conclusions. But the belief *is* a myth. In actual practice, no observations are as objective as anything qualified by the adjective "scientific" is supposed to be. The human mind will selectively see only what it wishes to perceive. After all it is not a camera that records everything in its field of view but perceives nothing at all. On the contrary, it is like the human eye, which is a highly selective receptor in what it chooses to "sense" and transmit and what it decides to ignore and suppress.

Since human mind is highly selective, one may almost say that truth like beauty is in the beholder's eye and not out there in the external world. It is, therefore, not surprising that even creative scientists are not immune from a great deal of subjective bias in their scientific theorising as autobiographical records of actual discoverers like John. D. Watson in his Double Helix clearly show. History of science is littered with highly subjective dead theories based on "observations" that never were. A case in point in genetics itself is the so-called

homunculus or manikin seen by the Dutch microscopists in the human sperm. See Fig. 9. Although the difficulty of

Fig. 9

drawing the boundary between observation and invention still persists, scientists are nevertheless well-known for their "objectivity" and solicitude for objective truth. Their reputation for "objectivity" and "truth" is due to operation *in reverse* of the Brutus aphorism:

*The evil men do lives after them*
*The good is oft interred with their bones.*

It is otherwise with scientific theories. It is the false and subjective theories which die in course of time that are buried in the limbo of oblivion. The true ones, which survive because of their objectivity, alone are preserved and kept alive. But living scientists who design experiments or spin theories of their own are known to select their core ideas out of the many possible ones for other than purely scientific reasons—aesthetic, emotional, moral and even metaphysical. If they happen to hit "right" ideas on which to build their experimental or theoretical work, they spark a breakthrough.

Mendel had the inspiration to guess the "right" breakthrough sparking idea of heredity, namely, that the genotype

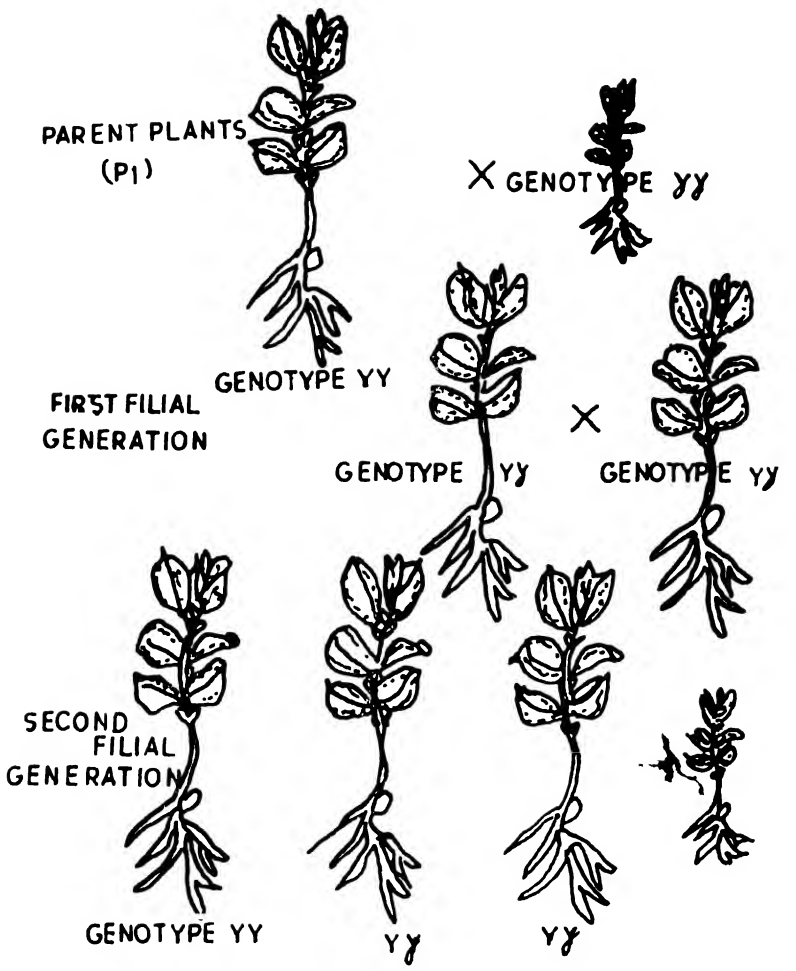
consists of discrete hereditary units which are passed from parent to progeny without "dilution or blending". It is doubtful if this epoch-making idea could have been suggested by his experiments; quite the contrary. After attempting to reconstruct Mendel's experiments R.A. Fisher found that Mendel's ratios are consistently close to expectation than sampling theory would lead one to expect. It is as though Mendel knew the answer before he started and was producing a demonstration like Galileo formulating his laws of falling stones before experimenting with an inclined plane. Although Fisher's analysis of Mendel's data makes it hard to explain how his data came to be as they are. the fact remains that Mendel was right after all. The truth about heredity dwelt in the deeps and Mendel was the first to see it. Having seen it, he proceeded to demonstrate it by designing appropriate breeding experiments to verify the bold hypothesis he had made. He did so by leaving out of consideration the greater part of the characteristics of the organisms with which he was working and concentrating entirely on one or two sharply marked features instead. In this way he proceeded to consider the phenotype as a set of a few elementary characters even though an organism is obviously not a mere assemblage of isolated anatomical structures and physical traits. Having thus considered genotype as a set of discrete "factors" (genes), on the one hand, and phenotype as an assemblage of visible traits to which they lead, on the other, he inferred the relation between hereditary consititution and appearance of an organism embodied in his laws from a few well-designed breeding experiments.

Mendel performed his celebrated experiments by growing a variety of peas in his monastery garden nearly a century ago. His typical oft-quoted experiment consisted in crossing tall-growing pea plants with short ones. He observed that the offsprings of the cross were all tall. He, therefore, concluded that when parents differ in character, the offsprings resemble one parent but not the other. In other words, one trait dominates the other. This is not to say that the dominant trait suppresses completely its submissive or recessive counterpart. For when Mendel used the first generation hybrid plants to breed the

next, he found that the second generation plants consisted of *both* tall and short plants in the ratio of three to one. In other words, the short trait reappeared in the second generation having remained dormant in the first. This led him to formulate his first law of heredity called the law of segregation. It merely states that when the hybrid reproduces, it transmits with equal frequency either the dominant trait of one parent or the recessive one of the other, but not both.

However, Mendel's experiments dealt with not only a single pair of contrasting traits like tall versus short plants but a few other similar pairs such as round versus wrinkled seeds and red versus white plants, etc. at the same time. He found that each pair of contrasting characters shows dominance and segregation independently of the others. This is Mendel's second law of independent assortment. These two laws of Mendel are the basis of modern genetics. Armed with our new knowledge of the mechanism of heredity outlined in the last two chapters, we may restate Mendel's laws and their underlying rationale in modern vocabulary.

Consider, for the sake of definiteness, Mendel's experiment with tall and short pea plants already cited. If we call the gene determining the size of the plant Y, there will be located somewhere in the appropriate chromosome pair in the body cell of the organism two variants of this gene because the initiating zygote has two sets of chromosomes one each from either parent. Let us call the variant or allele that produces tallness Y and the allele for shortness y. The genotype of the tall and short plants of the first parental generation ($P_1$) in Mendel's experiment may then be denoted by the symbols YY and yy respectively. Now the parent with genotype YY produces gametes carrying only Y, and, the other parent with genotype yy, gametes carrying only y. Consequently all the offsprings of the first filial generation ($F_1$) obtained by their mating will be of the genotype Yy having received the allele Y from one parental gamete and the allele y from the other. Since the character tallness is dominant and prevails over its recessive counterpart, shortness, the first generation ($F_1$) plants are all tall as shown in Fig. 10. If we now breed a second generation ($F_2$) by self-fertilization of the tall hybrids, then obviously there can only




Segregation in the second filial generation of the factors controlling tallness and shortness in pea plants

Fig. 10

be three kinds of genotypes in the second generation, according as the two size-determining genes in the offspring are both Y or both y or one Y and the other y. There is clearly no other combination possible. Accordingly the genetic constitution of the second generation population ($F_2$) will be fully described by the proportion or percentage of individuals

belonging to each kind of genotype. These proportions or relative frequencies are called genotype frequencies.

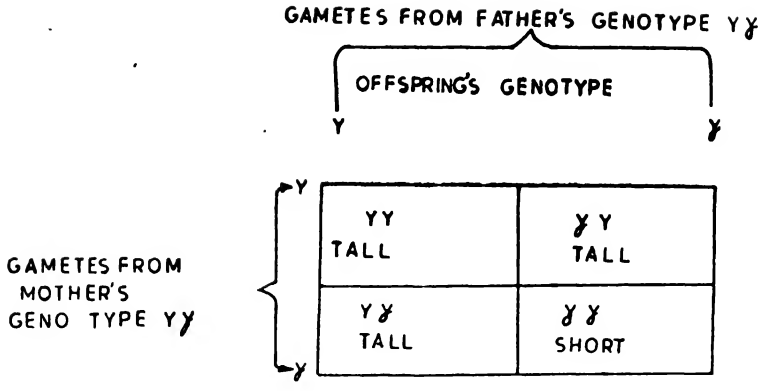
To compute the genotype frequencies we observe that each offspring produced by self-fertilizing the hybrids Yy receives only one gene from either parent. There are, therefore, four possibilities in all as follows:

| | *genotype* | *phenotype* |
|---|---|---|
| Y from father and Y from mother | YY | tall |
| Y from father and y from mother | Yy | tall |
| y from father and Y from mother | yY | tall |
| y from father and y from mother | yy | short |

Since it is immaterial for the genotype Yy whether Y is received from father or mother, the two permutations Yy and yY really yield only one genotypic combination. Further, if the mating in the population is random, all these four possibilities are equiprobable. It, therefore, follows that probability or frequencies of occurrence of these three genotypes YY, Yy, yy are respectively $\frac{1}{4}$, $\frac{2}{4}$, $\frac{1}{4}$, their sum adding up naturally to unity. It will be observed that while the gene probability or frequency of each allele Y and y is $\frac{1}{2}$, Y being as likely to occur as y in random matings, the probability of the three genotypes YY, Yy, yy to which they lead are respectively $(\frac{1}{2})^2$, $2(\frac{1}{2})\frac{1}{2}$, and $(\frac{1}{2})^2$. It will also be observed that while the genotypes YY and Yy are different, their corresponding phenotypes are the same. Both yield tall plants. This is why the observed frequency ratio of tall to short plants is $(\frac{1}{4}+\frac{2}{4}):\frac{1}{4}$, or 3:1 as shown in Fig. 10.

We may also exhibit the aforementioned argument more compactly in the form of a matrix or chequerboard which yields at a glance the genotype and phenotype frequency ratio of the progeny of a cross.

As a glance at Fig 11 will show, there are only four equally probable ways in which genotypes of the offspring of the cross (Yy) x (Yy) can arise. Two of them are the same genotype (Yy) so that there are three distinct genotypes which yield only two phenotypes due to dominance of the allele Y over y. The three genotypes are YY, Yy, and yy which appear in the ratio 1:2:1. But the two phenotypes tall and short are in the ratio 3:1,




There are three genotypes but only two phenotypes in the ratio 3 tall : 1 short

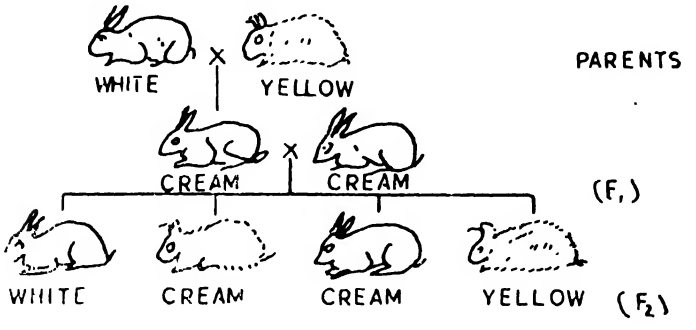
Fig. 11

since the two genotypes YY and Yy have the same phenotype, tall.

Although the phenotype of the genotypes YY and Yy is the same, genetically they are quite distinct. The former is called *homozygote*, while the latter containing different alleles Yy in the gene pair is called *heterozygote*. Obviously the genotype yy which produces short plants is homozygote because it contains identical alleles yy like its tall counterpart YY. It will now be evident that dominants can be of two genetic types either homozygotes like YY or heterozygotes like Yy; but recessives can be of only one type yy for they must always be homozygous.

The binary classification of genes into two types—dominants and recessives—is, however, a simplification of a vastly complicated state of affairs. For there are also genes neither of whose alleles completely dominates the other. The result is that the heterozygote is phenotypically distinct from the dominant homozygotes, so that there are three phenotypes instead of only two when one allele completely dominates the other. A case in point is the gene that determines the coat colour of guinea pigs. It has two alleles which we may denote by the symbols Y and y. The homozygotes YY have coat colour

white, while homozygotes yy are yellow. The hybrid Yy obtained by mating yellow with white is neither white nor yellow but cream. If we now breed a second generation by mating together the cream hybrids, there are produced, as before, three genotypes YY, Yy, yy in the proportions 1:2:1. See Fig. 12. But there are now three distinct phenotypes—white, cream and yellow—instead of only two when Y completely



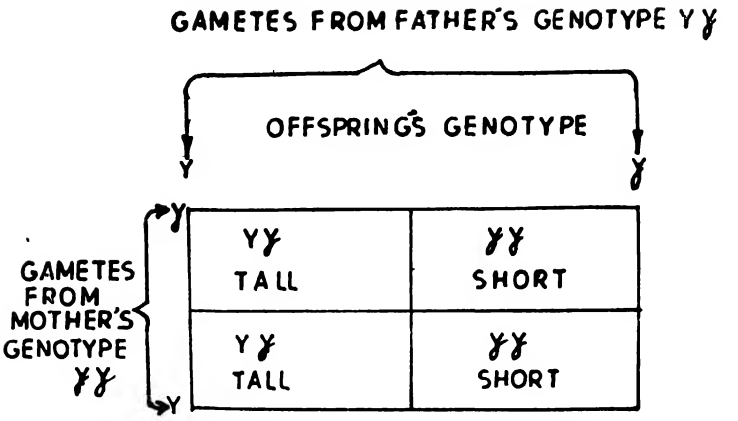

FREQUENCY OF THREE PHENOTYPES

Fig. 12

dominates its recessive allele y. However, in both cases whether dominance is complete or partial the *gentope* frequencies remain the same, namely, 1(YY):2(Yy):1(yy).

The aforementioned genotype frequencies are the result of a mating between two hybrids or hetrozygotes. It is also necessary to consider the highly important situation in which one parent is a heterozygote while the other is a homozygote. Using the same trait as before, tallness versus shortness, we find that the genotype of the tall heterozygote is Yy while that of the short homozygote is yy for only short plants being recessive can be homozygous. Using the chequerboard method as before, we observe that the offspring will now be of two genotypes Yy yielding tall plants and yy producing short plants in equal numbers. See Fig. 13. The genotypes are two: Yy (tall) and yy (short) in equal proportion.

We can also mate the heterozygote Yy with homozygote

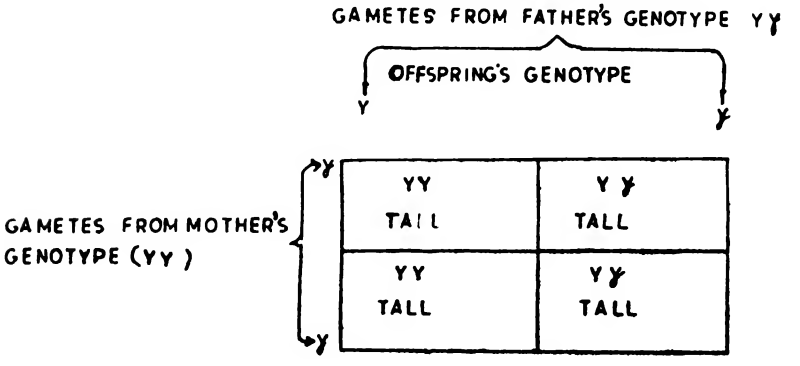



The genotypes are two Yy (tall) and yy (short) in equal proportion

Fig. 13

YY. The result will be the same, namely, equal proportion of two possible genotypes YY and Yy. But both types will now be tall since every genotype contains the dominant allele Y. See Fig. 14.

The simple type of mating shown in Fig. 13, or, Fig. 14, which arises by crossing a hetrozygote of the first generation with




Genotypes are two in equal proportion but phenotype is only One; all tall

Fig. 14

one or other of the parental homozygotes, is called a "back-cross". It is so called because it leads back to the parental form used in the mating. The individuals produced by a back-cross constitute what is known as an $R_2$ generation.

The back-cross is an important device for determining the genetic constitution of an individual during experimental work on animals and plants as we shall observe more fully in chapter IX. For it enables us to decide whether the $F_1$ generation carries two dominant alleles or whether one dominant and one recessive. But it is always desirable to cross it with the recessive type only. The reason is obvious. A back-cross with the dominant homozygotes is always masked by the emergence of a single phenotype due to dominance as all offsprings of the mating look alike even though they belong to two distinct genotypes. On the other hand, recessives are of known constitution, being necessarily homozygous and, therefore, allow demonstrable segregation of recessives as well as dominants among their offsprings when mated with hetrozygotes.

Our analysis so far has been confined to the segregation of a *single* pair of genes upon the basis of Mendel's first law. But when we consider the behaviour of two or more pairs of genes together we have to invoke his second law of independent assortment of genes. According to Mendel's second law when two or more pairs of genes segregate simultaneously, the distribution of any one of them is independent of the others. Suppose we consider now another pair of contrasting traits such as round versus wrinkled seeds. If the dominant allele which produces round seeds is denoted by R and its recessive variant producing wrinkled seeds by r, the genotype of the hybrid will then be Rr. The mating of the hybrids Rr will, as before, produce three genetical types RR, Rr, rr in the ratio 1:2:1. But there will be only two phenotypes, round or wrinkled, in the usual 3:1 ratio. However, the segregation of R genes will occur quite independently of the segregation of Y genes considered earlier. There is no tendency for the parental combinations of R and Y genes to be preserved in the offsprings, nor for the two dominant and the recessive types to segregate together. The upshot is rather a mathema-

tical melange of *two* 3:1 ratios. That is, the four diverse phenotypes that result will appear in the ratio 9:3:3:1 as we shall now show.

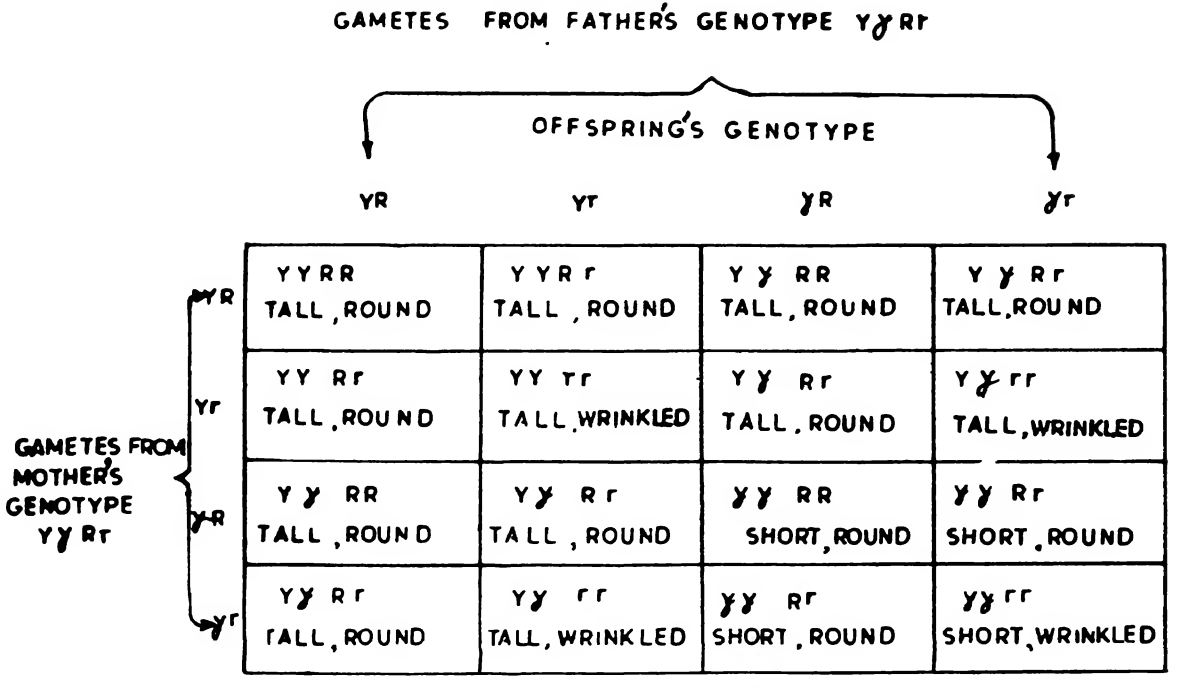
Since tallness and roundness are the dominant traits, the double homozygote dominant YYRR is a tall plant with round seeds. Such plants produce gametes possessing one member of each allele pair. They are, therefore, all alike, carrying both Y and R. Similarly, the double recessive yyrr, which is a short plant with wrinkled seeds, produces gamates all equipped with y and r. If we mate the individuals of these two types, we produce an $F_1$ generation which must consist of a single genotype, the double heterozygote of the constitution YyRr and these manifesting the two dominant states will be tall plants with round seeds.

Consider now a mating in which the partners are similar to this $F_1$ generation. Each partner will give rise to four kinds of gametes, carrying YR, Yr, yR, yr, in equal numbers. These four gametic types can be combined in $4 \times 4 = 16$ possible ways as illustrated in Fig. 15. But they give rise to only four phenotypes owing to dominance. It will be observed that nine recombinations contain at least one dominant member of both pairs of alleles, namely, Y as well as R. Consequently, they are tall plants with round seeds. Three possess rr and at least one Y so that they are tall plants with wrinkled seeds. Another three possess yy and at least one R yielding short plants with round seeds leaving only one double recessive type yyrr, a short plant with wrinkled seeds. These four groups, therefore, arise in the ratio 9:3:3:1 which represents their frequency in the second filial ($F_2$) generation as already mentioned. The same ratio may also be obtained more simply from the fact noted earlier that it is a mathematical melange of two independently combining 3:1 ratios. Thus if we denote tall and short plants by the symbols T and t and round and wrinkled seeds by W and w, the *combined* 3:1 ratios of the four traits are given by the product $(3T + t)(3W + w)$

$$9\,TW + 3Tw + 3tW + tw$$

(tall, round) (tall, wrinkled) (short, round) (short, wrinkled)

That is, the four possible combinations of the traits appear in the ratio 9:3:3:1.




These are nine genotypes but only four phenotypes.
Fig. 15

Fig. 15 also shows the form of segregation which would ensue in the absence of dominance. All the genetically distinct classes would then have been separable. They are the following nine genotypes:

YYRR, YYrr, YyRR, YYRr,
YyRr, yyRr, Yyrr, yyRR,
yyrr

If we count the number of each of these nine genotypes shown in Fig.15, we shall find that they appear in the ratio of 1:1:2:2:4:2:2:1:1.

As before. it is important to examine the situation arising from a backcross involving two independently assorting alleles. We know that the double heterozygote YyRr, being a tall plant with round seeds, must produce four types of gamets YR, Yr, yR. yr in equal numbers. Also the double recessive homozygote yyrr, producing short plants with wrinkled seeds, can produce only one type of gamete yr. It, therefore, follows that the mating of the two must yield in all four classes of offsprings, tall and round, tall and wrinkled, short and round, short and wrinkled. Since this is a back-corss constituting an $R_2$ generation, these will segregate in equal numbers as illustrated in the lowest horizontal line of Fig. 15.

We have now analysed the working of Mendel's second law in both of the fundamental genetic situations; those provided by the ($F_2$) generation and the back-cross ($R_2$) generation. For this purpose we have considered only the simplest situations when only one or two pairs of alleles are segregating. But the second law applies equally when three or higher numbers of allele pairs are involved. It can be shown that the tri-hybrid ratio, that arising from a union in which both parents are heterozygous for three pairs of alleles, leads with dominance, to the combination of three 3:1 ratios independently, that is to say, to the ratio of 27:9:9:9;3:3:3:1. This may be shown by the same matrix method we have hitherto employed. But it is more easily derived by computing the terms in the triple product (3T+t) (3W+w) (3C+c) where C and c denote respectively the dominant and recessive colour alleles in the red and white-flowering plants. We find that

(3T +t) (3W+w) (3C+c) =

(9TW+3Tw+3tW+tw) (3C+c) = 27TWC+9TwC+9tWC+ 9TWc+3Twc+3tWc+3twC+twc = 27 (tall, round and red)+9(tall, wrinkled and red)+9(short, round and red)+ 9(tall, round and white)+3(tall, wrinkled and white)+ 3 (short, round and white)+3(short, wrinkled and red)+(short, wrinkled and white).

In other words, there are now eight different phenotypes appearing in the ratio 27:9:9:9:3:3:3:1 though there are 27 different genotypes. In the absence of dominance each of these twenty seven distinct genotypes would produce a separate effect.

However, a mating between the triple heterozygote, Yy Ww Cc,manifesting all three dominant characters, and the triple recessive yy ww cc will yield eight distinct phenotypes in equal numbers. For this is a backcross in respect of all three factors. We thus observe that Mendel's second law provides an opportunity for bringing together genes which have arisen separately. This is obviously of great value to breeders of cultigens because it allows advantageous characteristics possessed by different stocks and races to be combined in the same individual. But unfortunately the possibilities of creating such favourable gene pools in actual practice are rather restricted because the "independent assortment" postulated by Mendel's second law has been found to have many exceptions. The reason is that it is not genes that are assorted independently but packages of genes we have called chromosomes. If two dominant genes Y and R are originally together in the same chromosome, they will tend to remain together.

For all practical purposes the two factors then assort together and behave as if they were one. Such factors and their sponsoring genes are said to be linked. *Linkage* is thus the tendency of two or more pairs of alleles to assort together, instead of independently according to Mendel's second law, because they are carried in the same pair of chromosomes. Although linkage is an exception to Mendel's second law, it is real grist to the geneticist's mill. For it is by study of linkage that geneticists have been able to explore the topology of chromosomes and make chromosomal maps as we shall show in the next chapter.

## CHAPTER IV

# *Linkage And Chromosomal Topography*

AS we have seen in the previous chapter, Mendel's second law of independent assortment of genes does not always ihold. It has been found to have many exceptions. It is not unlikely that some of Mendel's own observations failed to conform to his second law. But he had the serendipity to ignore them. Had he not done so, it is all but certain that he could never have divined the riddle of heredity as he actually did. But the gift of vision to see way beyond one's contemporaries often has its nemesis. It leads to complete neglect of one's work in his own life time—a misfortune that actually befell Mendel. His classical paper of 1866 reporting his epochal discovery was completely ignored for over thirty five years. When at long last it was rediscovered around 1900 by three eminent biologists who chanced on Mendel's paper, it set the bilogical world agog experimenting to see whether Mendel' laws applied to other living beings including man. Experimental results piled by investigators proved a mixed bag. In many cases Mendel's laws did seem to operate. But in many others the results were either inconclusive or flatly contradictory. The confusion in which the biologists were then beginning to flounder would have continued but for the emergence of

T. H. Morgen, who happened to become intensely interested in the little banana fly called *Drosphila melanogaster.*

Morgan found the banana fly an ideal subject for his experiments. For the Drosphila mother is nubile at the age of 12 days and within another 12 days produces some three hundred offsprings. Consequently starting from scratch, one can breed thirty generations per year – as many as we humans breed in a millenium. Moreover, the fly is a simpler organism having only a few pairs of chromosomes (only four against 23 in man) but many easily distinguished variations.

By experimenting with Drosophila, Morgan was able to prove that while the basic Mendelian laws held firmly, the mechanism of heredity was not as simple as Mendel had suggested. He and his brilliant corps of student collaborators—Herman J. Muller, Colvin B. Bridges, A.H. Sturtevant and others—discovered many complicated forms of gene operation. In particular, they discovered that exceptions to Mendel's second law arise not because Mendel's basic discovery was wrong, but because he was not aware of the fact that many of what he called "factors" and we call "genes" were packed together in packages we now call chromosomes. Consequently it is not individual genes that are assorted independently but whole packets of genes, that is, chromosomes.

Consider, for the sake of illustration, two heterozygous alleles Aa and Bb which are carried in the same pair of chromosomes. Let us first suppose that A and B lie in one of the homologous pair of chromosomes and a and b in the other. Consequently the genotype of the double hybrid individual may be represented by $\frac{A\ a}{B\ b}$ where each symbol denotes a chromosome of the homologous pair and the letters enclosed within it the genes or alleles it contains. At meiosis the homologous chromeosome pairs separate carrying $\frac{A}{B}$ together into one half of the gamete and $\frac{a}{b}$ into the other. On the other hand, homologous pair $\frac{a\ a}{b\ b}$ can give rise to only one kind of gametes which carry $\frac{a}{b}$. On a mating between these two

types, a back-cross generation is produced consisting of only two classes, $\frac{A\ a}{B\ b}$ and $\frac{a\ a}{b\ b}$ instead of four classes which should arise with independent assortment.

Now suppose the genes had been differently arranged in the double heterozygote, A and b being carried on one chromosome and a and B on the other yielding the genotype $\frac{A\ a}{b\ B}$. On mating with the double recessive $\frac{a\ a}{b\ b}$, which produces gametes of only one type, there arise again two classes instead of the expected four. But this time they are $\frac{A\ a}{b\ b}$ and $\frac{a\ a}{B\ b}$.

The two situations we have considered are rather different. In the first case, the dominant genes A and B were carried together in one chromosome of the double heterozygote and the recessive ones a and b were carried in the other. This is to say that the two dominants were linked in one chromosome and the two recessives in the other. On crossing with the double recessive, that same association is preserved, for only the double dominant and double recessive types appear. Such a situation where the double dominants and double recessives remain together is called *Coupling*. In the second situation one dominant and one recessive are carried in each homologous chromosome. This condition is also preserved in the segregating backcross family, which contains two classes of individuals only, possessing one dominant and one recessive character each. But unlike the former case one dominant character does not appear in the same individual as the other. As a result the dominants and recessives seem to be repelled from each other. Such a situation is therefore called *Repulsion*. In short, if the two dominants are originally together, they tend to remain together in subsequent breedings, a phenomenon we have called coupling, whereas if they were originally apart, they tend to remain so, a condition we have called repulsion. Both coupling and repulsion are only two sides of the same coin called linkage.

Nevertheless, the linkage between genes located on the same chromosome is not absolute. Thus if two genes A and B are located at different points of the same chromosome, they

would usually be linked together in one chromosome in the cells of the descendants. But sometimes through breakage and rejoining of the chromosome threads, the two genes may get separated, so that A would be on one chromosome and B on another. Thus if an organism is doubly heterozygous for two linked genes $\frac{A\ a}{B\ b}$ most gametes would be $\frac{A}{B}$ or $\frac{a}{b}$ but a proportion would be "crossover" types $\frac{A}{b}$ or $\frac{a}{B}$ and these if used in the production of the offsprings would be recognised by the new combinations of characters produced.

A specific example will explain more clearly the notion of crossover. Let A be the gene for eye colour and B that for the wing shape in the case of banana fly, *Drosophila melanogaster*. Since the normal conditions of red eyes and straight wings are dominant over the recessive traits pink eyes and curled wings, the genotype of the double dominant homozygote with red eyes and straight wings is $\frac{A\ A}{B\ B}$ whereas that of the double recessive homozygote with pink eyes and curled wings is $\frac{a\ a}{b\ b}$. If the two are crossed, all the offsprings ($F_1$) will have red eyes and straight wings like their normal parents but their genotype will be the heterozygote $\frac{A\ a}{B\ b}$. When females from such hybrid offsprings are mated to monozygote male flies with pink eyes and curled wings, a backcross ($R_2$) generation consisting of 50 per cent of flies with red eyes and straight wings—the hybrid $\frac{A\ a}{B\ b}$—and 50 per cent flies with pink eyes and curled wings—the pure bred double recessive $\frac{a\ a}{b\ b}$ *should* arise. But in actual practice there is a slight deviation from this theoretical anticipation. The percentages obtained are 49 instead of 50, the remaining two per cent being made up by flies with red eyes and curled wings and with pink eyes and straight wings in equal proportion. These last two represent the recombination, or crossover, classes. Added together, the crossover value between the pink and curled factors is 2 per cent, see Fig. 16.

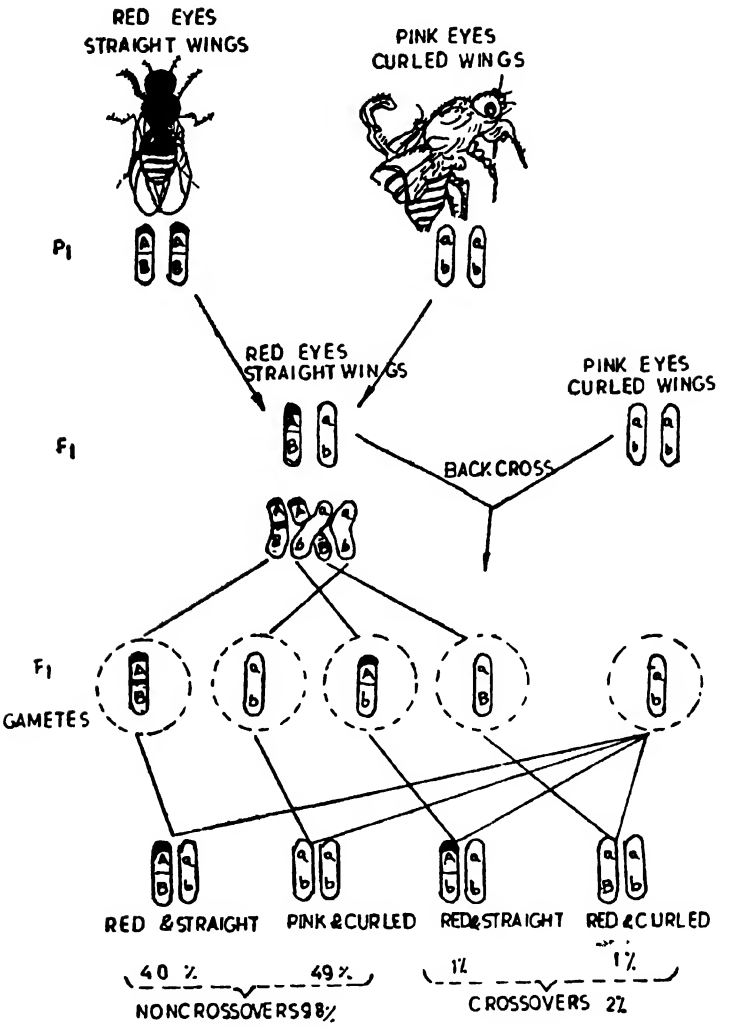



Fig. 16

Now if there were no "crossovers", the hyterozygotes $\frac{Aa}{B\ b}$ of F1 generation produce gametes $\frac{A}{B}$ and $\frac{a}{b}$ in equal proportion

whereas the monozygotes $\frac{a}{b}\frac{a}{b}$ produce only one type of gametes, namely, $\frac{a}{b}$. Consequently the two genotypes $\frac{A}{B}\frac{a}{b}$ and $\frac{a}{b}\frac{a}{b}$ should arise in equal proportion. But since crossing over occurs between them in two cases out of 100, it is obvious that the crossover gametes $\frac{A}{b}$ and $\frac{a}{B}$ formed are one per cent each. This is why one per cent of the flies belong to the two aberrant types, red eyes and curled wings in one case and pink eyes and straight wings in the other. These two types, which represent a harking back to the grand parental traits, are called the *recombination classes*. Together they measure the percentage frequency of crossing over. It is called the crossover value and is obtained by adding together the two recombination classes and expressing them as a percentage of the total number of offsprings. In the instant case the crossover value is two per cent.

The example just described is one of coupling. But crossover value is measured in precisely the same way in case of repulsion as well, namely, by adding together the recombination classes, though these are not the same as before. In either case the deviations in the expected frequencies of $R_2$ generation arise because of an interchange of linked genes consequent upon a reciprocal transfer of blocks of material between homologous chromosomes.

Since all the genes carried on a particular chromosome are, of course, linked with one another, it is possible to assign the linked genes of any organism to a series of groups. Thus there are four pairs of chromosomes in banana fly. Consequently all its genes belong to one or other of four groups. In general, the number of linked groups of an organism equals the number of *pairs* of homologous chromosomes in its cells. Furthermore, when the pairs of homologous chromosomes differ from one another considerably in length, the size of the linkage groups varies roughly in proportion.

An important offshoot of linkage theory is that the degree or strength of linkage depends upon the distance between the

linked genes in the chromosome. Obviously the further apart the two linked genes are in the chromosome the more likely would they be to cross over. Consequently we could measure the distance apart of two genes on the same chromosome, in a relative manner, by the frequency of the crossover between them. The idea has proved very fruitful. It has been developed into the theory of the linear arrangement of genes in the chromosomes and has led to the construction of genetic or linkage maps of chromosomes. Thus suppose we have three linked genes A, B and C resident in a single chromosome. If we measure the three crossover ratios between A and B, B and C, and A and C, we may find that the crossover value between A and C equals either the sum of the crossover values between AB and BC or the difference between them. This condition can only be satisfied by a linear relationship demonstrating that the genes are carried in a linear series along the chromosomes. Moreover, it allows the correct order of the genes to be ascertained. For if the crossover value between AC equals the sum of those between AB and BC, then obviously B lies between A and C. But in case it equals their difference, then C must lie between A and B. In this way the relative location of linked genes in a chromosome can be determined. To illustrate if A, B and C are respectively the three genes in the banana fly called ruby eye (rb), cut wing (ct) and vermillion eye (v), the crossover values between AB, BC and AC are found to be 16.7%, 14.5% and 31.2% respectively. Since the sum of 16.7 and 14.5 equals 31.2, it follows that the gene B must lie between the genes A and C. We may thus map the three genes on the chromosome as shown in Fig 17.

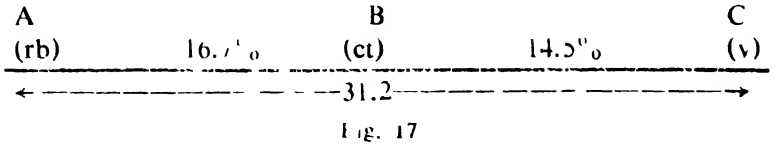
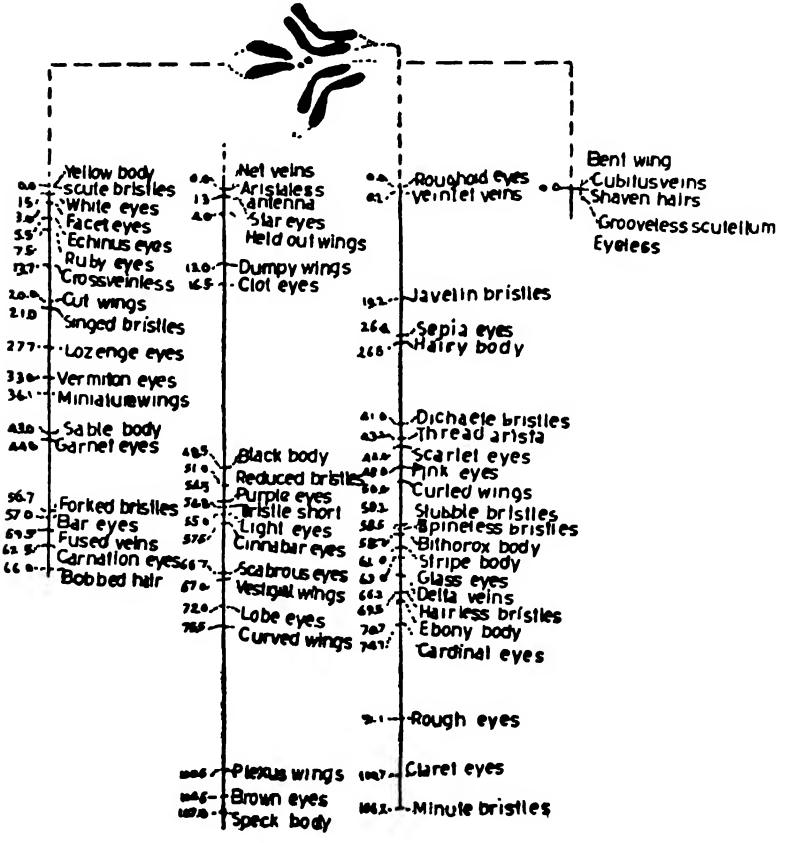



Fig. 17

This is only a stray illustration of the vast amount of work that has been done on linkage in a number of organisms notably banana fly and maize. It is this type of work which

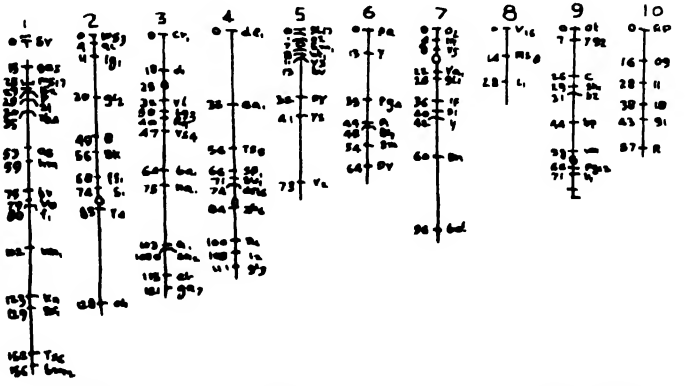
has enabled us to draw detailed chromosomal maps indicating the relative location of various kinds of genes in linkage groups. Fig. 18 is a genetic or linkage map of the four chromosomes of banana fly showing the relative position of some of the more important genes. Numbers represent *relative* distances from the upper end of the chromosome as determined by crossover values or percentages of recombinations in




A genetic or linkage map of the four chromosomes of Drosophila melanogaster, showing the relative positions of some of the more important genes Figures refer to distances from the upper end of the chromosome as determined from the percentages of recombination observed in linkage experiments.

Fig. 18

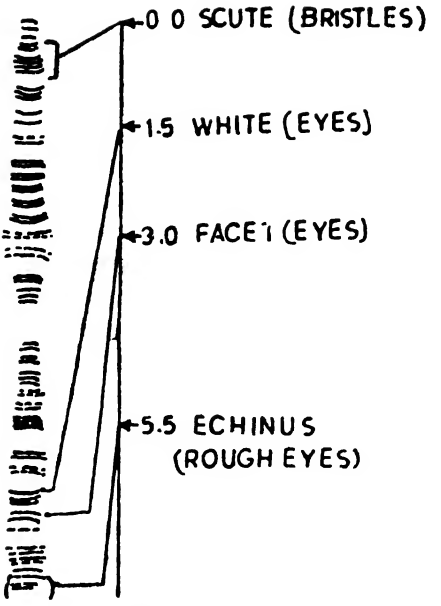
linkage experiments. Fig 19 is a similar linkage map of the ten chromosomes of the maize plant, which is the most extensively mapped species after the banana fly.




Linkage maps of the 10 chromosomes of corn, showing the arrangement of the most important genes.
(Courtesy: H.H. Rhoades)

Fig. 19

Such maps give us only the *relative* distances separating genes. They do not indicate the *actual* distances or locations of genes in a chromosome. For the map is based entirely on per cents of crossover, not on a direct examination of the physical chromosome under the microscope. It is a *crossover* map. However, it is also possible to determine the actual locations of genes in a chromosome by other means. This might be done, for example, by first removing a small segment of a chromosome by means of X-rays, then determining which genes had been removed by means of genetic tests. We might then examine the chromosome under the microscope to see what segment had been removed. In this way it is possible to show that certain genes corresponded with certain segments thereby locating the gene within the physical chromosome. A map which shows the actual location of genes in a chromosome involves not only the microscopic examination of the chromosome but also previous genetic analysis in the form of linkage tests. Such a map is known as a *cytogenic map*. Fig 20 shows a cytogenic map of a segment of the first




Section of a cytogenic map of a chromosome of Drosophila melanogaster alongside its corresponding chromosome map showing the location of only four genes.

Fig. 20

chromosome of Drosophila alongside its corresponding chromosome map for comparison. The figure indicates only the first four genes for purposes of illustration. It will be seen that the order of the genes is the same in both the maps. The relative distances in the two maps also generally conform. This conformity between the linkage groups inferred from breeding experiments and the chromosomes observed directly under the microscope is good evidence in favour of the chromosome theory of heredity. More exact proofs of the latter are provided by certain structural modifications of chromosomes and consequential altered behaviour of the genes located on them. Among these modifications or aberrations are deficiencies (loss or absence of a portion of chromosome), inversions (rotations of a chromosome through 180°), duplication (presence of an extra chromosome so that certain

regions are present three times instead of twice), and translocutions (exchange of parts between non-homologous chromosomes) all of which occur in nature.

Both the chromosome and cytogenic maps are the outcome of the cooperative work of many geneticists and plant breeders in order to gain knowledge of the precise topography of the molecular entities, the genes, lodged within chromosomes. Such knowledge is, no doubt, necessary for a proper understanding, of the mechanism of heredity as a prelude to its control by genetic manipulation. But though necessary it by no means suffices to suggest *predictive* ways of securing such control and producing profitable genetic manipulations of plants and animals.

The possibility of genetic manipulation was first mooted on the discovery that "engineered" gene replacements are feasible in simple unicellular organisms like the bacterium *Escherichia Coli*, which is normally present in human as well as various other vertebrate intestines ordinarily harmless and only occasionally pathogenic. It has been extensively studied by microbiologists during the past several decades. They have found it to be a typical rod shaped bactrium, which is only 3 $\mu$m long by 1 $\mu$m in diameter, 1 $\mu$m being one thousandth of a millimetre. It too possesses a very complex hereditary apparatus consisting of linked genes packed in a chromosome. In 1946 J. Lenderberg and E.L Tatum showed that recombination of genes from different strains of *E. Coli* may be achieved by a a number of processes, some of which resemble the sexual fusions of gametes in higher organisms, while others involve a transfer of genetic material from cell to cell via the exterior, a process that has not yet been successfully accomplished in any higher organism. We shall deal with such genetic transformations of one strain of bacteria into another more fully in chapter XII. Meanwhile we may merely remark that there is a fundamental difference between lower organisms like unicellular bacteria and multi-celled higher plants and animals in two respects. First, being single celled there is no separation between soma (body) and germ plasm in the case of the former. Consequently exchange of genetic meterials between the cells of bacteria is no indication that similar transfer is possible in the case

of higher organisms like plants and animals. Second, the arrangement of genes in animals is very different from that in unicellular bacteria like *E. Coli.* The last great breakthrough from genetical studies of unicellular organisms was the discovery of DNA molecule, the repository of genetc information. As we shall show more fully in the next chapter V, this information is embodied in the DNA molecule in three-letter words or condons made up from different combinations of the four different chemical subunits of DNA. Each condon spells out one amino acid of a protein chain. This view of gene and genetic information storage was derived from work on bacteria, single celled orgasisms.

During the past few years or so genetics has advanced from the genes of bacteria to those of multicellular animals. Recent work on these higher animals has shown that their genes are not linear strings of condons, as is the case with bacterial genes. They are strings punctuated by long stretches of DNA that do not code for anything. They are, to use communication lingo, mere "noise" punctuating or interrupting the true "signal". These noisy interruptions, the so-called *introns* are generally ten times longer than the "signal" or coding sequences named *exons* that they interrupt. Our genes thus seem to be made up of signals punctuated by noise or nonsense. Only the two are not mixed so that the noise does not drown or vitiate the genetic signal.

The punctuated DNA of higher animals has given rise to the natural question as to how did these punctuations get into the genes and why ? A very plausible answer seems to be that punctuated gene arrangement vastly increases the probability of combining exons, the genetic signal carriers, in different ways. It would, therefore, enormously accelerate the rate at which animals could evolve to perform the highly specialised functions on which their lives depend. For example, vertebrates would have been wiped out by disease at their first appearance had they not evolved antibodies to kill invading pathogens. And the structure of antibodies suggests just the kind of shuffling of coding genes or exons that is quite unlikely without their punctuation or interruption by introns.

In short, punctuated genes serve as vital an evolutionary

role as sexual reproduction. The latter permits an enormously greater variety of genotypes or genetical moulds than would be possible otherwise. In a somewhat similar fashion punctuated or split-gene can form a far larger number of genetic sequences for the production of an equivalent variety of proteins than would be the case without it.

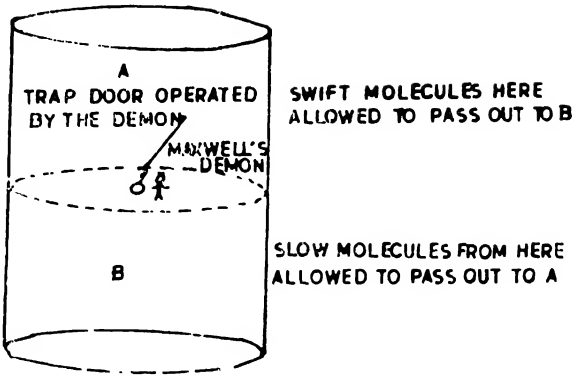
But punctuated genes of higher animals and plants are not the only additional complexity. There are many more. The most serious one is that being multicellular they must be studied at three levels : (a) the molecular level, (b) the cellular level and (c) the level of the organism as a whole. There are further complications due to diverse interrelationships between these levels. It, therefore, seems that the whole basis of the fantasy called "genetic engineering" is far too flimsy to warrant the belief that spectacular breakthroughs in the production of cultigens far superior to those now being produced are around the corner. We need to know much more about the heredity as well as cytology of plants and animals to manipulate their biological inheritance to our advantage in any meaningfully *predictive* way. We can come by such knowledge only by very careful combined work by geneticsts. biochemists, animal breeders, agronomists and many other specialists—work which in its early stages will appear too academic and abstract to be of any immediate use. It will take long before it can be applied. Meanwhile we shall have to remain content with such piecemeal improvements as the practical breeders of plants and animals can devise with growing assistance from geneticists. We shall revert to the topic in chapters IX, X, XII and XIII.

# CHAPTER V

# *Genetic Information*

ALTHOUGH scientific knowledge is power, the power it confers is strictly circumscribed by certain limit laws which Sir. E.T. Whittaker once called the postulates of impotence. One such postulate is the second law of thermodynamics. It asserts the impossibility of making a *Perpetuum mobile*, a perpetual motion machine that provides eternal power without any input of work or energy. The celebrated physicist, J.C. Maxwell, envisaged a way in 1871 to circumvent the second law by postulating a sentient being of molecular dimensions since nicknamed Maxwell's demon. He began his argument by assuming that the demon's "faculties are so sharpened that he can follow every molecule in its course, and would be able to do what is at present impossible for us. Let us suppose that a vessel is divided into two portions, A and B by a division in which there is a small hole, and that a being who *can see the individual molecules* opens and closes this hole so as to allow only the swifter molecules to pass from A to B, and only the slower ones from B to A. He will thus without expenditure of work raise the temperature of B and lower that of A in contradiction to the second law of thermodynamics". See Fig. 21.

Since the demon's sorting activity results in concentrating swifter molecules in B and the slower ones in A, and since,




Maxwell's demon

Fig 2'

moreover, temperature is merely a measure of the average speed of the moving molecules in a region, clearly B, the new niche of the faster molecules will be at a higher temperature than A, the rendezvous of the sluggards. But such *effortless* segregation of the molecules of a gas into a warm and cold region could provide a basis for constructing a *perpetuum mobile*. For we could make heat flow from the warmer B region of the vessel to the colder A to obtain mechanical work as in the operation of a steam engine. In other words, the demon is able to trade *information* for *power*. He decreases the "mixedupness" of the molecules in the vessel, that is, their disorder or *entropy* by sorting them into swift and slow molecules on the basis of information regarding their speeds and thus creates a temperature gradient which can be made to yield mechanical work.

Now the second law of thermodynamics forbids any such effortless gain of work or energy as Maxwell's demon is seemingly able to produce. In fact, we cannot gain anything for nothing not even an observation as G. Gabor has recently reminded us. What then is the fallacy in Maxwell's reasoning? Is it the impossibility of such sorting demons or even antomata like self-acting miniature spring valves that Maxwell invoked? Nothing is easier than to dodge Maxwell's paradox by affirming the *prima facie* impossibility of such beings. We

could, for instance, simply state that the demon being of the same size as the gas molecule cannot be "sentient" any more than gas molecules, or, even if it were, it cannot escape their random buffeting and thus stay put at the trap door to observe the speeds of approaching molecules. But if we adopted any such simple argument of its denial at the outset we would miss an insight into the deep connection that ties information and entropy. To begin with, is it actually possible for the demon or any automatic device to "see" the individual molecules? Although to decide the question we would need to probe rather deeply into the meaning of "seeing" at the molecular level, we may for our present purpose simply remark that an entity registers its existence in any "ego", whether animate being or an inanimate automaton, by the electromagnetic radiation (of which radiant light is but a minute fragment) that it emits. To be more precise, it is not the radiation emitted by an object that enables it to be seen but the difference between what it receives and emits. For an object not only emits radiation but also receives it from others. It is just the difference between radiation emitted and absorbed that makes its observation possible. If all objects in an environment radiated as much as they received from their neighbours, nothing could be observed there. Now a Maxwell demon at the trap door separating the two regions A and B of our vessel would be in such an unobservable environment where nothing could be perceived simply because he is in an enclosure where all radiation is in a state of equilibrium. That is, every molecule of the enclosure radiates as much to the walls as it receives from the walls so that it simply fades out of the observer's ken as he has no means of distinguishing them. The demon then must be provided with a means of "seeing" the approaching molecules such as an electric torch of microscopic dimensions. The torch is a source of radiation not in equilibrium and provides the *difference* in electromagnetic radiation required to observe the molecule.

Armed with such a microscopic torch, a source of some form of radiation not in equilibrium with its environment, the demon can "see" an approaching molecule and obtain

the information he needs to decide whether or not to open the trap door. The decrease in the state of "mixedupness" of the vessel which the demon's sorting into swift and slow molecules brings about is really reverse or negative entropy derived from the information that the illumination of the demon's torch yields. But as under quantum mechanics the energy of the illuminating photon must exceed a minimum, depending on the frequency of the radiation used for observation, the demon experiences a small recoil every time he lights the torch to emit the speed-probing photon, exactly as a rifleman does when he fires a bullet. As a result the demon is himself subject to a series of small random motions until, as Norbert Wiener has remarked, he falls into a "certain vertigo" that makes him incapable of clear perception. In other words, he no longer remains a Maxwell demon.

The longish detour we have followed in exorcising Maxwell's demon, rather than denying outright the existence of such a molecular homunculus capable of sorting and ordering, has a purpose. It points to a novel way of reconciling an apparent conflict between the second law of thermodynamics and the process of biological evolution. For the latter, with its continual emergence of ever new forms of life from inanimate matter does seem to lend towards increasing organization and "patternedness" of matter. On the other hand, according to the second law of thermodynamics, matter continues to drift towards a state of increasing chaos and "mixedupness". The physicist claims that the conflict is illusory. The march of our universe as a whole towards its heat-death doom of total disorder does not preclude the rise of order and organization here and there in some localized regions with an overcompensating loss of order elsewhere. He, therefore, views the eruption of biological order in myriad forms of life as a transient blossom in a vast erosion of free energy of which the most conspicuous manifestation is the enormous and continuous outpouring of stellar radiation in empty space. A tiny fraction of the immense downpour of sunshine from our own sun, for example, suffices to provide the wherewithal of all the biological order that reveals itself in the phenomenon of

terrestrial life. Some biologists, however, are inclined to the view that the thermodynamic principle of order is fundamentally different from the biological principle of organization, just as the alphabetical word order of a dictionary is very different from that of Roget's Thesaurus. Thus, if we connect two gas cylinders at different temperatures, in course of time they arrive at exact thermal equilibrium in accordance with the second law. From the physicist's point of view there was greater order or organization before the two cylinders were connected, for the swift-moving molecules were in one and the slow-moving ones in the other. After the two are connected, there is a complete shuffle between the slow and the fast-moving molecules resulting in greater chaos. But, as J. Needham has suggested, a biologist may well consider that the system has passed from asymmetry to symmetry. Needham concedes, of course, that it is a far cry from this simplest possible case of symmetry to the extraordinarily complex patterns of symmetry produced by animate beings. Nevertheless, he believes that "this apparently jejune idea" may be the first crude premonition of a "profound truth". A case in point is the spontaneous formation of crystals in a saturated solution. As is well known, the local enhancement of order represented by the assembling of the initially unordered molecules into a perfectly symmetrical crystalline network is compensated by transfer of thermal energy from the crystalline phase to the solution. There is a decrease in the overall free energy or order of the system in accordance with the second law of thermodynamics. But as the degree of order represented by even the simplest organism is incomparably higher than that of the crystal, the question arises whether or not the emergence of such an organism is also compatible with the second law. That this indeed is the case may be verified by recourse to an experiment closely analogous to that of crystallization.

If we plant a bacterium like *E. Coli* in a millilitre of water having therein a few millilitres of a simple sugar, such as glucose, as well as some mineral salts containing the essential elements that enter into the chemical constituents of living organisms (nitrogen, phosphorus, sulphur, etc.) the solution will contain inside thirty-six hours several billion bacteria. We

shall find that about 40 per cent of the sugar has been converted into cellular constituents, while the remainder has been oxidized into carbon dioxide and water. By carrying out the experiment in a calorimeter we can draw up the thermodynamic balance sheet for the operation. We find that as in the case of crystallization the entropy of the system as a whole (bacteria plus medium) has increased a little more than the minimum prescribed by the second law. Thus, while the extremely complex system represented by the bacterial cell has not only been conserved but has actually multiplied several billon-fold, thermodynamic debt corresponding to the operation has been duly paid. No definable or measurable violation of the second law has occurred. Nevertheless, as Needham has observed, the biologist, as a student of patterns, cannot but say that there is more order and organization in the well-arranged crystal than in its homogeneous mother-liquor and much more so in the more highly organised *E. Coli* colony than in the original nutrient medium. No possible conflict between thermodynamical order and biological organization can, therefore, arise, as the two concepts, are quite different and incommensurable. "Only as the time process goes on", Needham continues, "only as the cosmic mixing proceeds, only as the temperature of the world cools, do the higher forms of aggregation, the higher patterns and levels of organization, become possible and stable. The probability of their occurrence increases. The law of evolution is a kind of converse of the second law of thermodynamics, equally irreversible but contrary in tendency. We are reminded of the two components of Empedocles world, φιλία, friendship, union, attraction; and νεῖκος, strife, dispersion, repulsion".

Both points of view, however, though valid, seem to skirt the paradox rather than resolve it. The difficulty is not one of proving that there is available a vast reservoir of free energy in the form of sunshine, a small proportion of which serves as the ultimate motive power of all life on earth. It is rather how any given assembly of molecules, which is expected when left to itself to become more and more shuffled and disordered, does under certain circumstances begin to exhibit greater pattern and organization even though it is of an altogether

different kind from that envisaged by the physicist. In other words, the riddle of biophysics is to discover how the fortuitous concourse of myriads of blind and chaotic molecules while obeying the laws of physics and chemistry become at the same time integrated into organic wholes capable of entropy-decreasing animated activity. The problem, therefore, is to trace the very real differences in the behaviour of animate and inanimate matter to their objective foundations in some kind of spatio-temporal relationships. E. Schrodinger was the first to divine the nature of this difference when he formulated his "order from order" principle, which is "the real clue to the understanding of life". In the early forties when he wrote his book *What is life?* the molecular nature of genetic material was only dimly perceived. It was surmised that individual genes contained at most a million or so atoms, a number quite insufficient to account for the low rate of spontaneous mutation if the genetic material could be rearranged by random thermal collisions. The resolution of this apparent paradox, as we now know and as Schrodinger foresaw with remarkable clarity, is that genes are large macromolecules held together by quantum mechanical bonds of considerable strength. In fact, Schrodinger termed the gene "aperodic crystal", a remarkably apt and prescient description of the genetic material. Living things, therefore, differ from inanimate objects in producing "order from order" rather than decaying to a state of equilibrium characterised by maximum disorder or entropy as demanded by the second law of thermodynamics.

These earlier anticipations of Schrodingers have now been amply confirmed by biochemists. They have conclusively demonstrated the existence of giant macromolecules of biological materials which seem capable of decreasing "mixed-upness" or entropy of their environment. They do so in virtue of genetic information embodied in packages of genes we earlier called chromosomes very much as the punch card of a computer carries instructions for making it work in the desired way. In order that the punch card function as a source of information to guide the computer, it must be capable of spelling out specific messages in some alphabet just as letters of English alphabet make meaningful words and words in

turn meaningful sentences. Now the alphabet of the computer language is determined by the fact that it is essentially an assembly line of switches, relays or transistors. Each one of these components is capable of exactly two states, "on" or "off", which we many designate respectively as the "energized" or "stimulated" state, and the "de-energized" or "unstimulated" state. If we denote the former by 0 and the latter by 1, any input signal in such a machine is merely a sequence of 0's and 1's. That is, the alphabet of the machine language in which its "words" are written is the binary set of symbols, 0 and 1. Its physical embodiment is the punch card with a set of holes bored therein with the hole corresponding to "energized" state denoted by 1. That such a binary alphabet is adequate to write any message is obvious from the fact that a telegraphist uses precisely such a binary alphabet in transmitting any communication whatever via the morse code with its repertoire of only two symbols—a dash (0) and a dot (1). It is, indeed, the alphabet of cosmos in that if and when we happen to stumble on an extraterresterial intelligence it is the only one that can be used for establishing communication between them and us.

But just as a computer is an assembly of relays or transistors a living organism is a collection of cells made up mostly of natural polymers called proteins. It is these myriads of proteins that form the solid core of living substances, hence the name which is derived from the Greek word *Proteios* meaning "holding first place" in life processes. Proteins are large molecules composed of long chains of amino acids linked together by so-called peptide bonds. If we denote the known 20 amino acids by the letters B, P, Q, E, D, K. L, Q..... ..... a typical protein molecule could be expressed, for example, as

-B-P-E-D-K-O-O-Q-

The above chain is shown open at both ends because protein molecules are giants most of them having 200-1000 amino acids in each of them. The giant size is also responsible for their immense variety. For the number of different proteins that may be formed by various permutations of 20 amino acids is practically unlimited exactly as one may construct a

virtually infinite vocabulary (mere chains of letters) with a limited alphabet. Thus a fairly medium protein like haemoglobin that enables human blood to carry oxygen to body tissues and gives it its characteristic colour, contains about 600 amino acids. But the possible diversity of molecules of this size with twenty amino acids is theoretically $20^{600} \neq 10^{781}$, being the number of ways of filling 600 places when each place may be filled in twenty alternative ways. When it is recalled that the total number of particles in the universe according to the cosmologist Eddington is only $10^{79}$ (if we may use "only" in juxtaposition with such a gargantuan number), we may appreciate the vastness of $10^{781}$ and thus obtain an inkling of the quasi-infinite mutuability of protein structure and its properties. No wonder there are 100,000 different protein species in the human body itself and that the manifold of substances belonging to the protein family are as diverse as hair, nails, skins, bones, cartilage, muscle, connective tissues, nerve, fibre, blood haemoglobin, harmones, insulin, egg albumin, feathers, wings, shells of insects and so on.

The detailed description of the molecular structure of these diverse proteins is naturally a task of stupendous complexity. It is, therefore, not surprising that the chemistry of living organisms at the molecular level is still a mystery though we no longer believe the mystical rodomontades of the creative evolutionists and their allies the vitalists, that life processes are not explicable by physico-chemical laws. The mystery of life processes arises not because chemical reactions within living organisms are fundamentally different from those occurring in the laboratory; quite the contrary. It arises simply because life is a vast chain of self-sustaining chemical reactions catalyzed by minute proteinous substances called enzymes essentially similar to any ordinary chemical reaction in a laboratory which needs to be sparked by a catalyst. Enzymes function exactly as ordinary catalysts by reducing the activation energy of the catalyzed reaction. But they do so far more efficiently than inorganic catalysts and thus permit chemical reactions within animal bodies to take place at much lower temperatures. For example, to decompose hydrogen peroxide into water and oxygen requires 18 kilocalories per

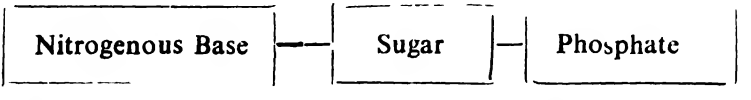
mole of hydrogen peroxide, catalytic iron brings this value down to 13 kilocalories, and platinum to 12 kilocalories. But the liver enzyme called catalase reduces it to less than 5 kilocalories. This is why the whole complex metabolic machinery of living cells is so utterly dependent on enzymes. It is the enzymes which mediate all cellular reactions which are otherwise similar to any chemical reaction in the laboratory sparked by a catalyst. The complexity of life processes that still baffles us lies in the vastness of the chain of interrelated chemical reactions but not in the nature of the individual reactions per se. Thus to account for the whole metabolic process of a single cell we require a thousand species of enzymes. The isolation of all the enzymes involved in the functioning of any particular type of cell is, therefore, even now an enormously complex task though by no means as hopeless as earlier biologists imagined. But all the complexity springs from having to dovetail into one consistent pattern a vast number of interrelated chemical reactions that are otherwise quite ordinary. They take place according to the usual physiochemical and thermodynamical laws and like all laboratory reactions are accompanied by certain transformations of matter and energy. Nor is there anything peculiar about this energy or matter. It is plain energy of everyday physics having no affinity with Bergsonian *elan vital* or Shavian life force, even as matter is ordinary commonplace matter.

Thus a living cell extracts the free energy it requires to maintain its inherently unstable and improbable organization by recourse to a sort of miniaturized combustion process in exactly the same way as an internal combustion engine provides us power from the chemical bonds of the fuel it burns. The only difference is the exceedingly low temperature at which it is carried out, so that life is quite literally an infinitely attenuated flame. The mechanisms of these subdued and smoldering fires of cellular combustion that sustain the processes of life have been studied in detail and found to conform in every respect to the fundamental laws of physics and chemistry including both laws of thermodynamics. Whether the cells obtain the energy they need directly from sunlight by the process of photosynthesis as do the chloroplasts

of green plants, or by respiration, that is, oxidation of prefabricated complex chemical fuels such as carbohydrates, proteins, and fats as in the mitochondria of animal cells, the same well-defined molecule—adenosine tri-phosphate (ATP) — carries the free energy extracted from foodstuffs or from sunlight to all the energy consuming processes of the the cell. In both processes of energy recovery— whether in the photosynthetic phosphorylation of the plant cells or the respiratory glycosis and Krebs citric acid cycle of the animal cells—the energy-loaded electrons are carried through a series of "electro-carrier" molecules of the mediating enzymes. Although all the "carriers" have not yet been fully identified, there is little doubt that the existence of disentropic phases within living matter, that is, phases leading to decreases of entropy, is due to a kind of sorting of energy-rich electrons by a large diversity of specific enzymes, which seem to be Maxwell demons of some sort decreasing entropy by a much more complex variant of the activity of their precursor of 1871.

Just as the Maxwell demon acted on the basis of information regarding the velocity of the gas molecule, the enzyme demons of the biochemist act on the basis of genetic information of great specificity that they receive at birth in a coded form. It has recently been shown that the chief carrier of the genetic information that tells the enzyme concerned what to do in the process of protein build-up is a substance called DNA short for deoxyribonucleic acid.

DNA as also its chemical ally RNA (ribonucleic acid) is, as the name implies, a species of nucleic acid. Nucleic acids like proteins are also highly complex structures being linear sequences *not* of amino acids but of altogether different subunits called *nucleotides*. There are three main types of nucleotides in a nucleic acid linked together according to the following arrangement:




The sugar in the middle is always of the same kind, a different kind in DNA and RNA. It is indeed the sugar of the DNA which makes the chromosomes recognizable when

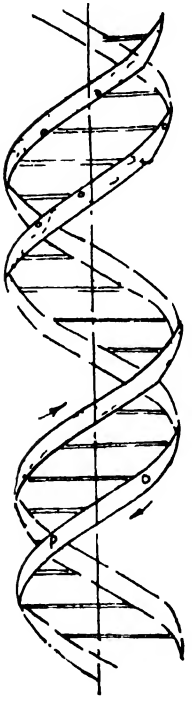
suitably stained. The nitrogenous bases are of four kinds. They may be denoted by the letters A, C, G, T, for DNA and by the letters A, C, G, U for RNA. Nucleotides chains may be single or double stranded. A single strand in DNA could be represented by

—A—C—C—G—T—T—A—G—C—T—

or, in RNA by

—A—C—C—G—U—U—A—G—C—U—

where U is the counterpart of T in DNA. For double-stranded DNA, the well known double helix made famous by Watson in his book of the same title (see Fig. 22), there is a simple



The double helix of Watson and Crick. This figure is purely diagramatic The two ribbons symbolize the two phosphate chains, and the horizontal rods the pairs of bases holding the chains together the vertical line marks the fibre axis (Nature, 1953).

Fig 22

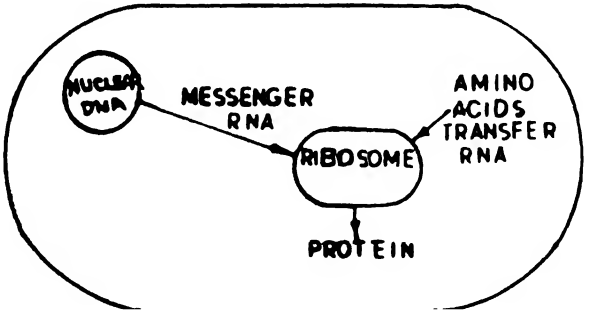
rule that A always pairs with T and C with G. Accordingly a portion of double-strand could be represented:

—A—C—C—G—T—T—A—G—C—T—
| | | | | | | | | |
—T—G—G—C—A—A—T—C—G—A—

Because A always pairs with T and C with G, if we know the

sequence of nucleotides in one strand, we can tell that in the other. All we need do is to replace A by T and C by G and vice versa. The discovery of the ways in which the sequence of the nucleotides—A, C, G, T—in the DNA of a chromosome is translated into the sequence of amino acids in a protein molecule is one of the outstanding achievements of molecular biology. It is our first peep into that universal language of life called the "genetic code" which is the same in all organisms from the lowliest virus to the highest man. If ever the microbiologists' "Central Dogma" that whatever happens in a bacterium like E. Coli will happen in an elephant is true, it is with regard to the alphabet and syntax of this universal language of life—the gentic code.

We shall begin our description of the genetic language by first spelling out its alphabet. The alphabet has been evolved to transmit genetic information contained in the nuclear DNA to the site of protein synthesis within the cell. This task is accomplished in four steps as illustrated in Fig. 23. First, the




An outline of protein synthesis

Fig. 23

double stranded DNA, the main repository of genetic information, multiplies by unwinding and building on to each single strand the complementary sequence nucleotides. Second, an unwound strand DNA attracts to itself the nucleotides of the A, C, G, U, series to produce a single strand RNA sequence that, as it were, transcribes the DNA information. It is called messenger-RNA or m-RNA. Third, the messenger-

RNA thus formed passes out of the nucleus into the cytoplasm and becomes attached to ribosomes, minute granules made up of protein and another type of RNA, which function to direct the 'translation' of m-RNA sequence into an amino acid sequence in a way roughly analogous to punch card of computer that carries the programme instructions. This "transcribed" RNA is called transfer RNA which is also a single stranded molecule. Fourth, transfer RNA carries out the protein synthesis from the surrounding pool of amino acids. There are twenty different varieties of such transfer RNA's each corresponding to twenty amino acids commonly found in proteins. The amino acids—transfer-RNA complex becomes attached to the ribosome with its messenger RNA molecule when the addition of the amino acid to the growing peptide chain occurs. This provides means by which the m-RNA transcript is 'read' from one end to the other with the concomitant construction of the right protein chain. In short, the information contained in DNA is first transcribed into an RNA molecule from which it is subsequently translated into protein conforming to the formula: DNA→RNA→Protein.

All the aforementioned steps can be carried out in the test-tube if the building blocks, enzymes and ribosomes, are provided as well as the nucleic acid to give primary information sequence. Indeed, this is precisely how the essential facts of protein synthesis within the cell were actually discovered. Similar experiments have even revealed the secret of genetic code, namely, the precise rules for translating a nucleotide sequence in DNA into a protein sequence via that in RNA. Since there are only four bases in both the nucleic acids DNA and RNA—A, C, G, T in DNA and A, C, G, U in RNA—minimum of three letter triplet is required to represent 20 amino acids. For four letters each taken singly can represent only four amino acids and when taken two at a time only $4X4=16$ amino acids. But since we can form $4X4X4=64$ different triplets out of our letters, their number is more than the necessary minimum of 20. It, therefore, happens that an amino acid is represented by more than one triplets. We will not dwell on the elaborate researches done to discover triplet equivalents of the twenty amino acids. Suffice it to remark that

a knowledge of the base sequence in the messenger RNA and the resulting amino acid sequence in protein gives away the code for each amino acid. The RNA triplet UUU, for example, is the code for the amino acid phenylalanine corresponding to the sequence AAA in the DNA. In this way the four letter DNA alphabet A, C, G, T is able to spell out the entire dictionary of myriad protein structures written in twenty letter alphabet of amino acids. The correspondence between DNA and RNA triplets and their matching amino acids is now available in tables as precise and universal as the multiplication table. Table 1 below gives the DNA and RNA triplets, or, condons as they are often called, for only four amino acids merely for illustrative purpose.

**TABLE 1**

The Genetic Code: Nucleotide triplets (condons) specifying different amino acids in protein synthesis.

| DNA Triplet | RNA Triplet | Amino Acid |
|---|---|---|
| AAA | UUU | Phenylalanine |
| AAG | UUC | |
| AAT | UUA | Leucine |
| AAC | UUG | |
| GAA | CUU | |
| GAG | CUC | |
| GAT | CUA | |
| GAC | CUG | |
| CTA | GAU | Aspantic acid |
| CTG | GAC | |
| TAC | AUG | Methionine |
| etc. | etc. | etc. |

To recapitulate, the information embodied in the DNA molecule according to the genetic code shown in Table 1 is conveyed to the sites in the living cell where proteins are actually assembled by means of transfer RNA. On the basis of information supplied by messenger RNA at the cellular

assembly sites amino acids are sorted out and brought into proper alignment to be linked together into protein molecules in a series of chemical reactions of great specificity. The proteins so manufactured, many of which are themselves enzymes, become the mediating agencies whereby the cell synthesizes a host of other molecules—purines, carbohydrates, fats, pigments, sterols and the like—necessary to its structure and function. Thus the tiny living cell is an extraordinarily intricate automatic chemical computer. The analogy is, no doubt, rough and remote but no more than other well known ones of animal physiology like the heart being a pump, lungs a pair of bellows, eyes a camera, stomach a fermenter, central nervous system a telephone exchange and so on. All such analogies no matter how rough and remote do have a degree of similitude that illuminates an aspect of their working. In the case of a cell we may summarise the preceding description of its working by the following statement: Although the precise mechanism of protein synthesis within the cell is not yet fully understood, its underlying principle does seem to be a cyclic transformation, of information into patterned organisation, order, or negative entropy ("negentropy") and of negentropy in turn into information like the action of Maxwell's demon in gas cylinder. The somewhat analogous activity of the nucleic acids suggests that they are threshold egos trading information (knowledge) for negentropy (power) thus demonstrating anew that knowledge is power as much *within* a molecule of life as it is *without* in the life of man.

# CHAPTER VI

## *Heredity and You*

JEAN Jaques Rousseau began his inimitable *Confessions* by complimenting himself with the remark that nature broke the mould in which he was cast. Had the findings of modern genetics been known in his day, he would have realised that this indeed was no great distinction. For each one of us—genius or dunce, prodigy or imbecile, beauty or beast, blonde or brunette—is cast in a genetical mould the like of which has never been in all history, nor shall ever be again in all eternity. The reason is that the process of casting genetical moulds or making what we have called genotypes is in some ways very similar to dealing card hands and there is actually more likelihood of a given bridge hand being repeated than that of duplicating the genotype of any given individual. First, this given individual is the result of mating just the specific parents out of all the myriads of the past and present, and he could have been produced by no others. But this is not all. These two specific parents could have theoretically produced some 70,000,000,000,000 different genotypes each different from any other in one or more ways.

The reason why such an astronomical number of genotypes can arise from a single couple is the fact that conception is merely the fertilization of a female egg by a male sperm.

When it occurs, the nuclei of both the sperm and egg fuse to produce a new cell which is, in fact, the genotype or genetical mould of that particular individual. To understand the mechanics of this mould-making process, imagine a pack of cards with four kings and two red queens removed. You will then have 46 cards grouped in 23 pairs, twelve black pairs beginning with a pair of black aces and ending with a pair of black queens and eleven red pairs beginning with

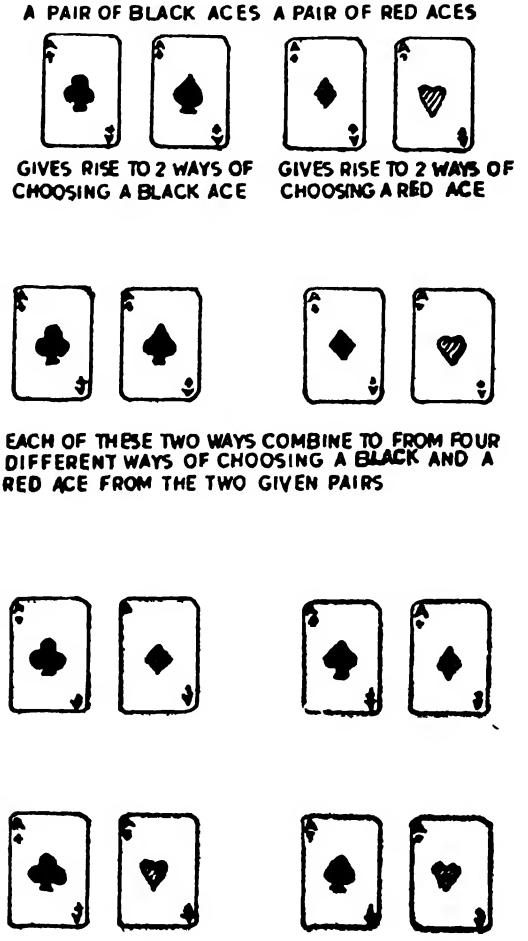



Fig. 24

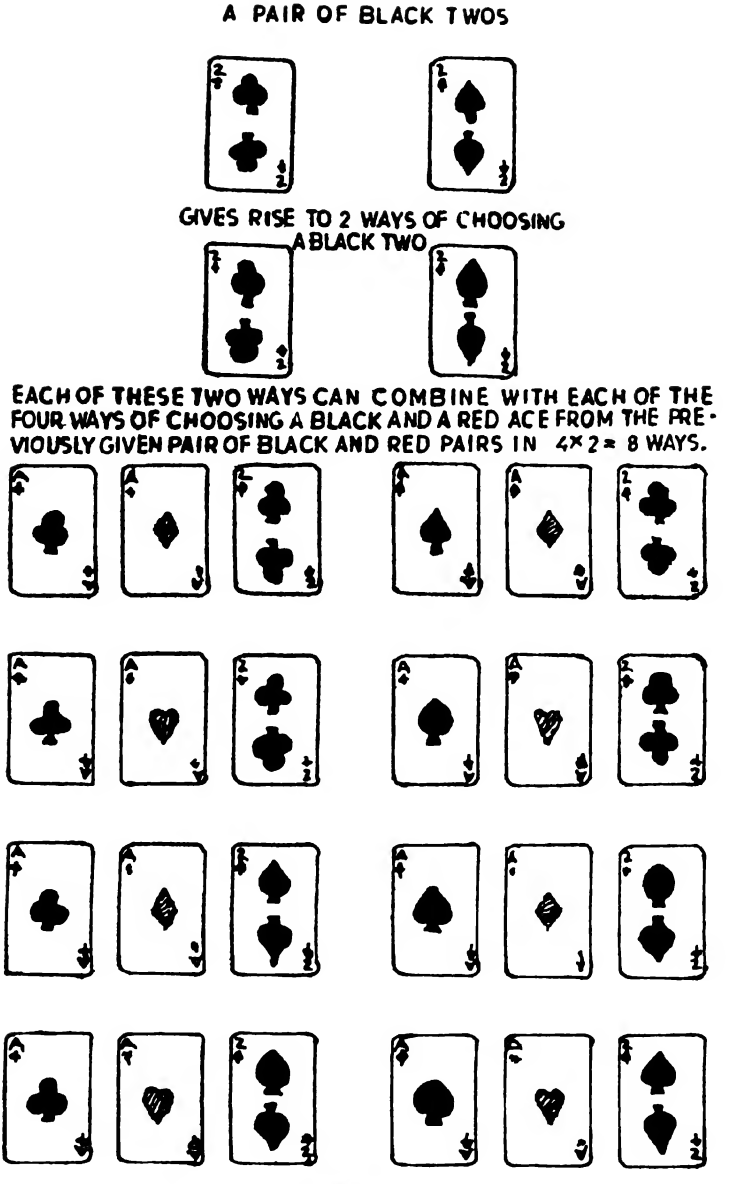

A PAIR OF BLACK TWOS
GIVES RISE TO 2 WAYS OF CHOOSING A BLACK TWO
EACH OF THESE TWO WAYS CAN COMBINE WITH EACH OF THE FOUR WAYS OF CHOOSING A BLACK AND A RED ACE FROM THE PREVIOUSLY GIVEN PAIR OF BLACK AND RED PAIRS IN 4×2 = 8 WAYS.

Fig. 25

a pair of aces and ending with a pair of jacks. Now pick up one card out of each pair, that is, either the ace of spades *or* clubs out of the pair of black aces and so on for all pairs of each denomination and colour. How many sets of 23 cards could you pick up in this way?

To simplify the problem let us first take a pack containing only four aces—two pairs in all, a black pair and a red (see Fig. 24). Out of the pair of black aces we could pick the ace of either spades or clubs. This gives two ways of picking a black card. Similarly, there are two ways of picking a card of the second (red) pair, and since each of the former two ways can be combined independently with the latter there are in all $2 \times 2 = 2^2 = 4$ ways of picking two cards out of four, as a glance at Fig. 24 will show. If you had three pairs of cards, two pairs of black and red aces and a third pair of, say, black twos, a similar calculation would show that you could pick up three cards out of the six in $2 \times 2 \times 2 = 2^3 = 8$ different ways (see Fig. 25).

It is not difficult to see that for every increase in the number of pairs in our pack the number of different ways increases by a power of two. So, out of the full pack of 46 cards of 23 pairs with which we originally started, we can pick up 23 cards in the manner described in $2^{23} = 8,3,88,608$ different ways. Now if we substitute chromosomes for the cards, we have a pretty close approximation to what actually happens when a sperm or egg is formed from a body cell by a process of cell reduction we called meiosis. For a human body cell consists of 23 pairs of different chromosomes very much as our pack of cards consists of 23 pairs of cards of the same denomination and colour. When it divides one chromosome out of each pair separates from its associate in the pair and the result is the production of two sperms (or ova) each containing 23 single chromosomes (Fig. 26).

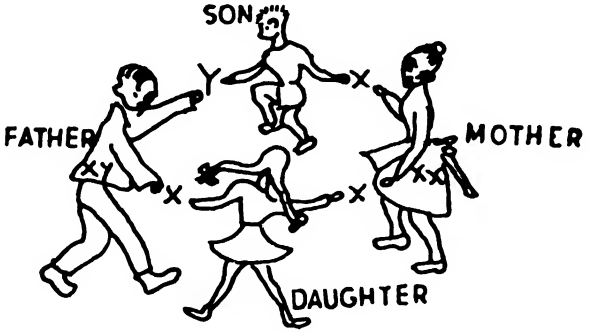
The process of sperm (or ovum) formation out of the germ cell by meiosis is thus closely analogous to that of picking 23 cards out of 46 in the original pack. This is why a sperm (or ovum) may be any one of the $2^{23} = 8,388,608$ different combinations of 23 chromosomes out of the 46 in the germ cell. But any one of these eight million odd different sperms


Fig. 26

may fertilize any one of the same number of possible ova at the time of conception to form a genotype consisting of 23 pairs of chromosomes. Consequently, the total number of different genotypes that any given pair of parents could theoretically make is $2^{23} \times 2^{23} = 70,368,744,177,664$ or in round figures 70,000,000,000,000. In other words, the chance of even a given pair of parents ever duplicating any one of these genotypes is so remote that it could happen only once in about $(70,000,000,000,000)^2 = 49 \times 10^{26}$ times. This is many million times *rarer* than duplicating a given bridge hand in a bridge game and about ten times *rarer* than dealing all the *four players a complete suit of cards.*

Although the number of distinct genotypes that even a single couple may produce is legion, they are only variations of a single basic theme. For every genotype in this astronomical collection is simply a set of 23 pairs of similar homologous chromosomes even as our analogical pack consists of 23 pairs of similar, that is, equal denomination cards like pairs of aces, twos, threes, etc. If we could arrange all the pairs in a line as we can our playing cards, they would look as shown in Fig. 26. It will be seen that the figure exhibits two arrangements—one for cells of females and the other for those of males. Both are alike in that each chromosome is matched with another to make a pair except that in the cells of males the last pair—pair number 23—is not properly matched. It is a mismatch because while one of the pair is a proper chromosome—it is called X-chromosome—its partner is

virtually a dummy as it carries very few genes. This dummy or atrophied chromosome, the so-called Y-chromosome is present exclusively in males. Every male offspring receives the Y-chromosome in its cell exclusively from the father simply because it does not occur at all in mother's cell, both of whose chromosomes in pair number 23 being X. Since mother's cells have two X-chromosomes, the eggs formed by her germ cells will necessarily contain one X-chromosome. On the other hand, since father's cells have X and Y-chromosomes, half the sperms produced by his germ cells will contain X-chromosome and other half Y-chromosome. An egg fertilized by an X-bearing sperm will produce a girl (XX) while that fertilised by a Y-bearing sperm will give rise to a boy (XY) (see Fig. 27). Sex is, therefore, wholly a genetical



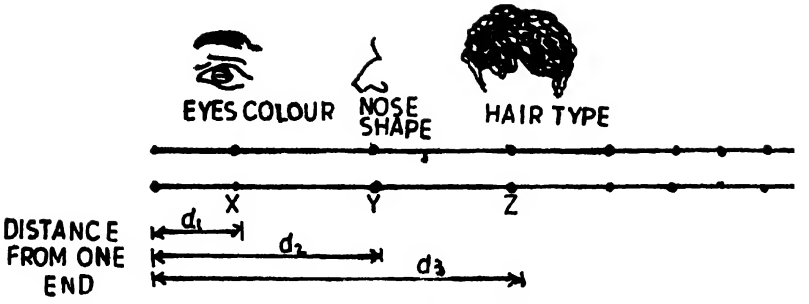

Transmission of the sex-chromosomes from parents to children.
The father gives an X to his daughter, a Y to his son. The mother gives an X to all her children. The son receives an X from his mother, a Y from his father. The daughter receives an X from both parents.

Fig. 27

effect regardless of environment. It is decided solely by whether an egg is fertilized by an X-or Y-carrying sperm. This is why X and Y chromosomes are called sex chromosomes. The remaining 22 "regular" chromosomes are called autosomes. Biological inheritance of *homo sapiens*, therefore, consists of 22 pairs of autosomes and a twenty-third pair of sex chromosomes which are alike in the female but unlike in the male.

Sex, however, is not the only attribute of offspring that is wholly determined by the genes it inherits. There are, for example, other traits like blood-group, skin and eye colour, hair colour and hair type (curly or straight) etc. which are also wholly dependent on inherited genes. Only we do not yet know enough about these things because of the inherent limitation of human genetics due to its being an intricately tangled mix of heredity and environment. Such a tangle can only be resolved, if at all, by resort to breeding experiments where either genetically different organisms are crossed, or genetically uniform organisms are reared under different conditions. Breeding experiments cannot be performed in the case of man where neither the control of genotype nor of his living environment or yet experimental crossing of different genotypes is possible. One has, therefore, to rely on indirect procedures like the study of families, pedigrees and large interrelated groups of individuals called populations or extrapolation of the general principles of genetics like Mendel's laws derived from the study of other simpler organisms such as pea plants and banana fly. Both procedures have been essayed to create the discipline called human genetics. It is still in its infancy. But when fully advanced it should enable us (a) to label by number or letter every individual gene carried by each chromosome and to specify its precise location therein and (b) to specify the role it plays in determining the genetical traits of the offspring produced.

For instance, we should be able to say that each of the chromosomes in the pair-number, say 12 consists of 500 genes and pair number 15 of 329 genes. We should next be able to locate these genes in the 12th and 15th chromosome pairs and to describe their roles. Since genes are known to be linearly arranged within chromosomes, the location of each gene is indicated simply by its distance from one of the terminals of the chromosome. Thus suppose genes x, y, z, . . . . within the 12th chromosome pair are concerned with traits like eye colour, nose shape, hair type, . . . . . respectively. Suppose further that they are located at distances $d_1$, $d_2$, $d_3$ . . . . from one end of the chromosome measured on some appropriate scale. We could then draw a simple line diagram as in Fig. 28.




A hypothetical chromosomal map showing the loci as well as the way the genes on a homologous chromosome *pair* are matched.

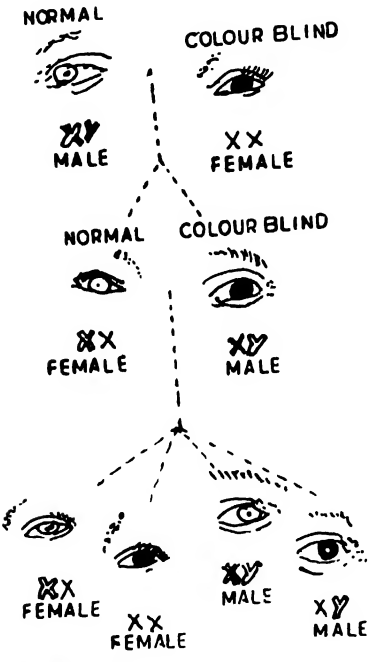
Fig. 2

to indicate the relative location or locus of each gene on the chromosome and the role it plays in determining the traits of the offspring that inherits them. These line diagrams called chromosomal maps, would then be more truly the fate lines of the individual possessing those chromosomes than the lines on one's palms so avidly studied by palmists to predict our future. A hypothetical chromosomal map embodying the aforesaid assumptions is drawn in Fig. 28 solely for illustrating what they would be like when human genetics comes of age to produce them.

The idea of chromosomal map of man is not as far-fetched as it may seem at first sight. Such maps have actually been drawn for simpler organisms like banana fly and maize plant which can be bred experimentally as well as more quickly than human beings. We have already seen in Chapter IV how they may be drawn on the basis of crossover values observed in linkage experiments in the case of banana fly and maize plant. Similar methods cannot obviously be applied to man. Nevertheless, a beginning has been made in constructing a linkage map of the two sex-chromosomes—X and Y—of man. They have been chosen because it is relatively easier to observe and measure linkage between genes required for the construction of such maps when the genes are located in sex-chromosomes than in autosomes. For the sex-chromosomes do not merely contain genes concerned with the sex-determination. They also carry many more genes affecting the widest range of characters

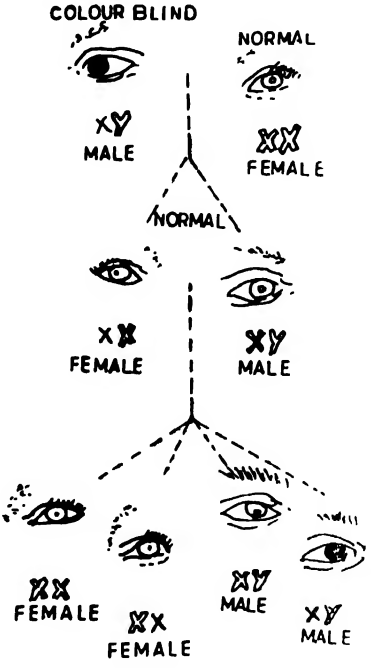
which bear no relation to sex except that being carried in the same vehicle with the sex genes they assort themselves together. Consequently, they are called "sex-linked genes" and the traits to which they give rise "sex-linked characters", owing to their association with sex. Being linked with sex the resultant phenotypes are more easily recognised.

A case in point is red-green colour-blindness which is the




Results of marriage of a colour-blind woman and a normal man where the defect is transmitted to all the sons and both the grandsons and granddaughters.
Colour blind individuals and chromosomes carrying the gene for this character are shown in black.

Fig. 29




Results of marriage of a colour blind man and normal woman where the defect is transmitted only through the daughters and appears in half their sons, being carried in one of the X-chromosomes.
Colour-blind individuals and chromosomes carrying the gene for this character are shown in black.

Fig. 30

commonest sex-linked trait. It occurs in about 5 to 8 per cent of men and only 0.5 per cent of women. It is inherited as a sex-linked recessive in the same way as other genes according to Mendel's laws. Let Cand c be the two alleles or variants of the gene concerned with colour-blindness. Since the condition colour-blindness is recessive to the normal condition, only the double recessives cc will be colour blind and both the double CC as well as heterozygotes Cc will be normal. It is now easy to see why colour blindness is found more often in men than in women if we recall that a father transmits X chromosome to all his daughters but none to his sons whereas a mother passes one of her two X's to each of her children no matter whether male or female. Accordingly all the sons of a colour blind mother are colour blind regardless of what kind of colour vision her husband may have (see Fig. 29). But if the husband has normal vision, all his daughters, will be normal even if his wife is colour blind. These daughters, however, will be carriers of the gene for colour-blindness since they contain the recessive (c) covered up by the dominant allele C inherited from the father. The carrier daughters, if married to men with normal vision, will have normal daughters but half their sons will be colour blind, the other half being normal. A colour blind daughter will be produced only if a colour blind man happens to marry a colour blind woman or a carrier. Since women who are either carriers or colour blind and colour blind men are less common than those with genes for normal vision, such marriages are quite rare (see Figs. 30 and 31).

Similarly, one of the forms of the disease hemophilia is restricted almost entirely to men who are invariably sons of mothers who are normal but are carriers of a recessive hemophilia gene. This hemophilia manifests itself chiefly in failure of the blood to clot when exposed to air. In normal persons such clotting limits the bleeding from wounds and thus prevents excessive and possibly fatal hemorrhages. In hemophiliacs, even a small skin injury can lead to death from excessive loss of blood due to the inability of the blood to coagulate. The hemophilac gene is, therefore, semilethal. Hemophiliac men, if they survive and reach the reproductive age, produce daughters

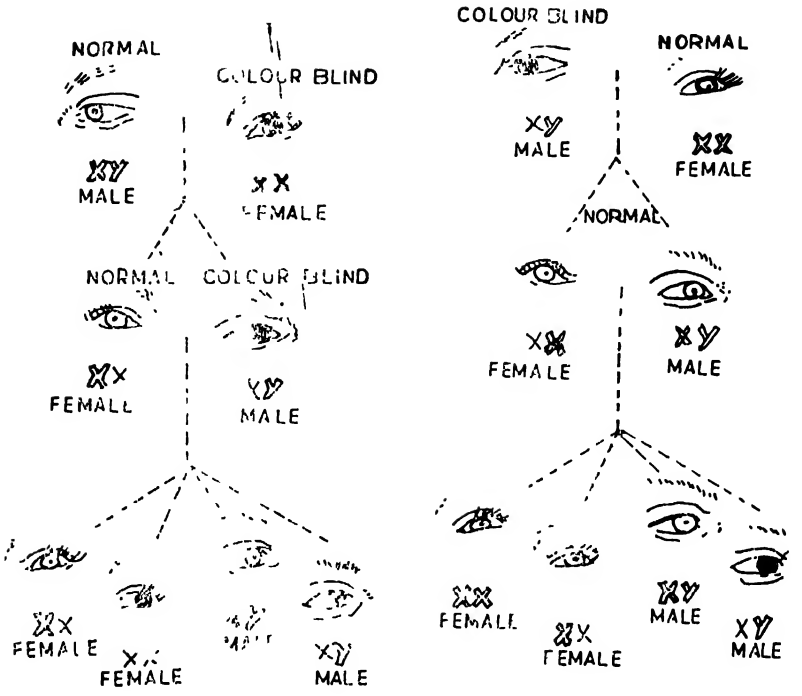



Fig. 31

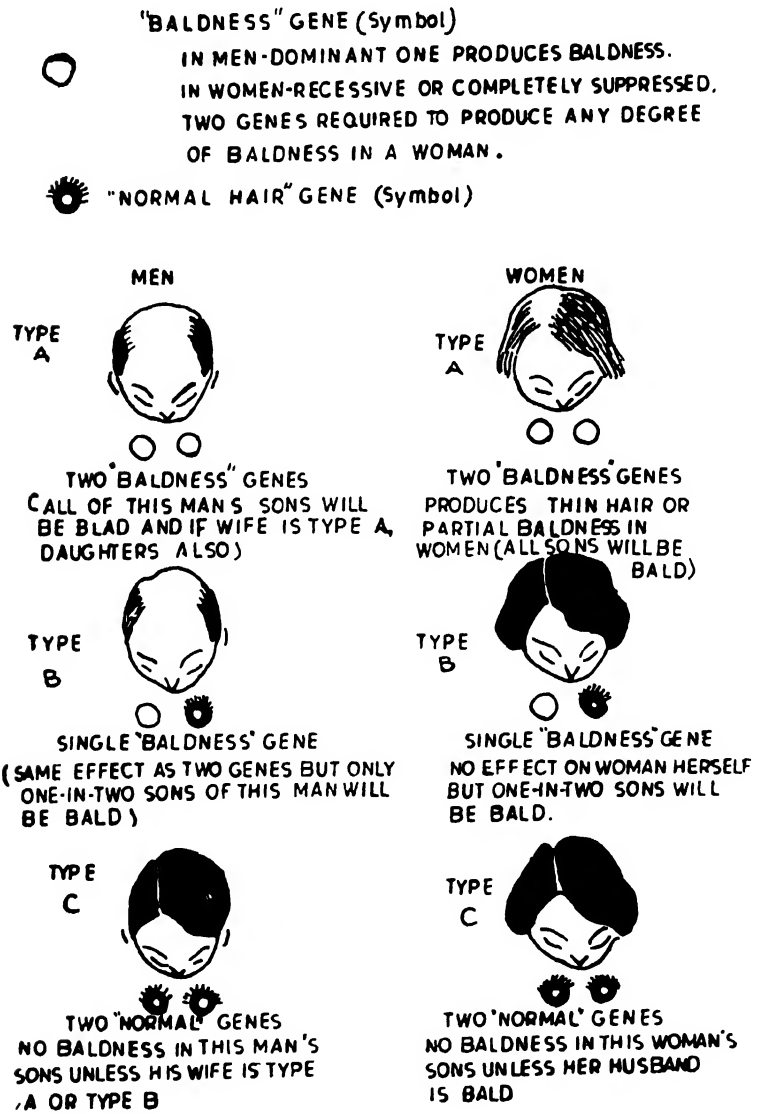
all of whom are normal but who are carriers of hemophilia, which they transmit to half their sons (grandsons of the male hemophiliacs) one-half of the daughters of the female carrier are, of course, also heterozygous carriers. Accordingly hemophilia gene is transmitted from a heterozygous carrier to her daughters, grand-daughters, etc. all of whom will have normal blood though half the sons they produce will be afflicted with hemophilia. A famous case of this sort is the transmission of hemophilia in some royal houses of Europe, which is traceable to Queen Victoria and her progeny.

Besides the sex-linked genes contained in X-chromosome for afflictions like colour-blindness and hemophilia, geneticists have also found a *sex-limited* gene which causes baldness. Unlike sex-linked genes, a sex-limited gene is not carried in the X-chromosome, but in one of the other 22 chromosomes

called autosomes common to both sexes. Thus the baldness gene can be inherited equally by a man or woman. But it does not act in the same way in both. It behaves like a dominant in a man so that only one gene suffices to make him bald. In a woman, however, it acts as a limited recessive. She must receive two baldness genes before she will be afflicted and even then only partial baldness or merely a thinning of hair may ensue. (see Fig 32). The reason is that although many genes conform to Mendel's fundamental rule that a given gene always expresses itself in exactly the same way in all individuals, there are many others which do not. They are the deviants whose effect on development varies with the individual carrying them. The existence of such deviants is not difficult to understand if we recall that a gene is merely a trigger that sets in motion a network of developmental biochemical reactions. If gene and effect are not related to each other directly, but through a sequence of numerous interconnecting steps, it is but natural that a change anywhere along the sequence of interconnections may lead to a change in the expression of the gene. In other words, a given genotype need not necessarily always give rise to a constant phenotype. This is precisely the case with the deviant baldness gene under consideration.

It happens that the glandular make-up of the two sexes governs the way the gene expresses itself. A woman lacks the excess of "male" hormones without which the gene cannot act and show itself. Some remarkable evidence to support this surmise has been given in studies and experiments by Dr James B. Hamilton. He administered "male" hormones to a large group of men who had been demasculinized through accident or injury, or who for biological reasons had failed to mature sexually. Where previously not one case of baldness had appeared among these men, the addition of "male" hormones resulted in the loss of hair among many of them particularly those from families in which baldness was common and were therefore putative carriers of baldness gene. On the other hand, no amount of "male" hormones will produce baldness in men lacking the baldness gene. This is merely to say that while baldness gene is fully penetrating in males, it is not at all or very little effective in females. The extent to which the

baldness gene produces its phenotypic effect is called *penetrance*. It is cent per cent in males but practically nil in females.




Inheritance of baldness
Fig. 32

There are many other genes with incomplete penetrance. A case in point is a dominant gene D that causes an affliction called blue sclerotic. The individuals inheriting the sclerotic gene have unusually thin outer wall on the eye which, therefore, has a bluish tinge instead of the white sclerotic of normals. The eye condition itself is harmless but it is often associated with serious defects in other parts of the body. Among these are a species of deafness and excessive fragility of the bones causing frequent fractures. Curt Stern cites the case of a young heterozygous man in Oslo with this gene, who "turning around suddenly in the street in order to look at the legs of a pretty girl, fractured his leg bone. Another time, when he took his fiancee on his lap, his thigh bone broke". It is not clear how the three abnormalities caused by it—bluish tinge on the eye, deafness and fragile bones—are developmentally related to one another. It could be either by some general metabolic condition that involves the mineral content of the blood or by control of fundamentally different processes in different parts of the body by the blue sclerotic. The gene effect on the fragility of the bone is not the same in all individuals. In one country only 63 per cent of the individuals inheriting the blue sclerotic gene showed its effects as fractures of the bones. It, therefore, follows that while the gene effect on the sclera itself has a very high, though incomplete, penetrance, it is only 63 per cent in so far as fractures due to bone fragility are concerned.

The term penetrance is applicable not only to heterozygously dominant genes like the blue sclerotic gene cited above but also to other dominant or recessive homozygous genotypes. This means that not only in the phenotypes of heterozygotes but also those of homozygotes it may vary. An example of incomplete penetrance of a homozygous recessive gene is provided by diabetes mellitus, the metabolic disease which leads to excretion of sugar in the urine. Certain data suggest that it is due to a relatively common recessive allele. Accordingly homozygous recessives carrying two such genes should be afflicted. But actually only 20 per cent of such individuals are diagnosed as diabetic. The remaining 80 per cent are so weakly affected that they show practically no sign of the

disease. It is, therefore, obvious that the penetrance of the recessive diabetes gene even in homozygous individuals is highly variable. Similarly, the penetrance of the recessive gene (t) causing taste-blindness for the organic compound phenylthrocarbamide (PTC) is highly variable. We now know that homozygous recessives carrying (tt) find PTC tasteless whereas homozygous dominants (TT) as well as heterozygous (Tt) find it bitter. Careful tests show that individuals who can taste PTC differ widely in their sensitivity to it: some can taste highly diluted solution of the substance, others can recognise it in only strong solutions. The causes of the variability in the taste reaction are manifold: there are racial differences, the same person will give different responses in different tests, responses differ in different age groups, and women are more sensitive tasters than men. In other words, the penetrance of all three genotypes TT, Tt and tt is variable. There are perhaps other autosomal genes responsible for taste in general. If so, their penetrance is even more highly variable making taste sensitivities in men and women as widely unlike as in the old Chinese legend about three sages who were asked to describe the taste of vinegar. The first philosopher said 'It is sour', the second, 'It is bitter' and the third none other than Laotse, 'It is fresh'.

The variable penetrance is not confined merely to autosomal genes, that is, genes carried in chromosomes other than sex chromosomes X and Y common to both sexes. It also applies equally to some of the sex-linked genes to which we shall now revert. Unlike autosomal genes, sex-linked genes like those responsible for red-green colour-blindness and haemophilia already mentioned occur *singly* in the X-chromosome without any partner allele in the Y-chromosome. This is why a male that carries a single dose of a recessive sex-linked gene shows its effect in the phenotype. But the Y-chromosome, which as we noted earlier, is a dummy, is not entirely empty of genes. It too carries a few Consequently the genes carried in the Y-chromosome will have their homologous alleles in the X-chromosome so that the XY pairing in the male presents situations different from that of the pairing of autosomes or for that matter the pairing of the sex chromosomes in the

female which carries two of X. If we stretch the Y chromosome along X-chromosome as in Fig. 33, we find that the

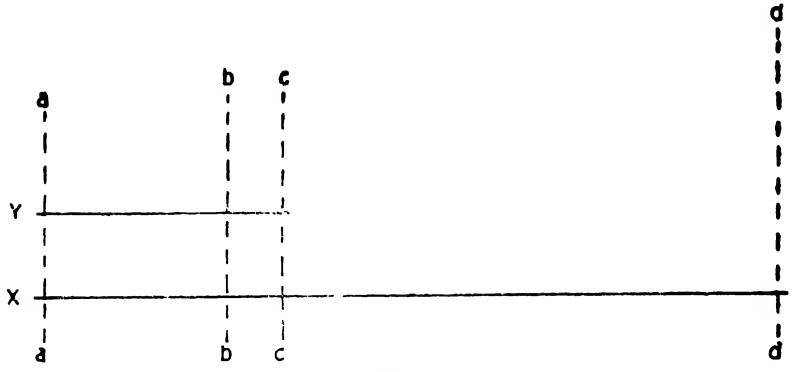



Fig. 33

larger X-chromosome may be divided into three segments. First, there is the short segment marked ab which contains homologous alleles in both X and Y-chromosomes. Next follows the still shorter section bc of the Y-chromosome containing material that has no counterpart or alleles in the parallel section of the X-chromosome. Finally, there is the greater part of the X-chromosome which stretches from c to d alone. The total non-homologous section of X-chromosome is therefore bc + cd = bd. It is this part of the X-chromosome that carries the colour-blind and haemophilia genes we considered earlier. They are known as *totally* sex-linked genes. This is the most usual type and is the one always intended when sex-linkage is mentioned.

Nevertheless, there are a few other rare traits which are also *totally* sex-linked because the gene in question is located in the non-homologous portion 'bc' of the Y-chromosome. Since this portion of the human Y-chromosome is very short, it must carry relatively extremely few genes. It is, therefore, no surprise that only two or three such genes have so far been detected. One of them is responsible for the production of webbed toes though several other genes carried elsewhere on the autosomes are also known to give rise to the same abnormality. Another instance of similar kind is the extra-

ordinary skin disease *(ichthyosis hystrix gravior)* in which the skin becomes thick, rugged, even bristly and blackened. It forms a tough cuticle which is shed at intervals, exposing skin which is at first normal but soon becomes thickened again. The affliction has been encountered only in a single family.

The progenitor of this unique family was one Edward Lambert born in 1716. At birth he appeared to be a normal baby born to normal parents who had many other children all of whom remained normal. But Edward began to show signs of an extraordinary skin affliction when he was barely seven or eight weeks old. His skin started thickening until his whole body—except palms, soles, head and face—was covered with rough bristly scales and cylinderical bristle-like outgrowths nearly an inch long. Edward Lambert was reported to have had six sons all afflicted with the same condition. The disability was said to have appeared in four later generations. But it was confined only to all the sons of an affected father but not to any of his daughters. Curt Stern, who verified the pedigree of Edward's progeny, is of the view that two daughters were affected. If so, the guilty gene could not be located in Y-chromosome. Be that as it may, the indubitable fact remains that such abnormalities as are caused by genes carried in the non-pairing region (bc) of the Y-chromosome are passed directly from father to son, and, of course, can only affect males. This is the sole inheritance restricted to one sex only; nothing comparable with it has been found, nor is it to be expected, in women.

In sharp contrast to total sex-linkage of the two types described above there also exists the case of *partial* sex-linkage because in the homologous regions ab of the X and Y-chromosomes each gene is matched by its allele in the other. Consequently partial sex-linkage differs from total sex-linkage in two ways. First, the genes in this region can be crossed over between the two chromosomes as in autosomes. Second, they possess alleles in both sexes instead of only in the female. These differences may be illustrated by a few examples. The disease, *retinitis pigmentosa*, involving a progressive degeneration of the retina due to deposition of pigment, is caused by two such *partially* sex-linked genes, one dominant and the

other recessive in effect. If the dominant gene responsible for the disease were totally sex-linked, that is. located in the bd region of the X-chromosome, men who suffer from the disease would transmit it to all their daughters and none of their sons. Actually, however, they may carry the guilty gene either in the X or Y-chromosome. If the former, sex-linkage of the normal type will ensue, except that occasional affected sons will appear, owing to crossing over between X and Y. In the latter situation, with the gene already in Y, the sons will be chiefly affected and the daughters free from the debility. But again exceptions may occasionally arise due to interchange of the gene in Y with its normal allele in X. The case of the recessive gene responsible for *retinitis pigmentosa* is a little less simple. Affected individuals must receive it from both parents. In the mother it must be carried in a X-chromosome, in the father it may be in X or in Y. In the former case when the gene is carried in paternal X-chromosome, half the daughters but none of the sons would be double recessive and therefore be afflicted. In the latter event, the reverse would be true.

Nor is *retinitis pigmentosa* of the aforementioned type the only known instance of recessive *partial* sex-linkage. There are many other pathological defects which are now known to arise in a similar way. We may cite two such examples. First is the skin disease called, *xeroderma pigmentosum*, characterised by a peculiar type of freckling, degenerating areas and cancerous growth which inevitably leads to premature death. It is inherited as a double recessive abnormality as far as the serious pathological effects are concerned. That is, the victims are invariably homozygous for this gene while the heterozygotes are normal people even though many of them do show freckling. Second is the case of congenital colour-blindness which is an exceedingly rare state usually associated with various minor ocular defects. It is a much more extreme condition than the ordinary red-green colour blindness.

It is these partially sex-linked abnormalities like *retinitis pigmentosa* and congenital blindness associated with genes in the pairing part (ab) of the X-chromosome that have been employed to construct chromosomal map of X and Y pair. For only homologous genes located in this portion can

possibly cross over from one to another and thus permit detection and measurement of linkage between them. As we saw, the crossover value provided by the linkage is an index of the relative distance the gene is located from one end of the chromosome so that it is possible to construct a map of the pairing portion (ab) of the sex chromosomes showing the loci of these genes. This has actually been done by Haldane whose chromosome map indicates the actual order of five of the known genes upon the chromosome and provides an estimate of their relative distances. See Fig. 34.

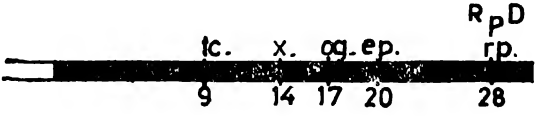



Fig. 34 Map of the pairing portion of the human sex-chromosomes, showing the position of five of the known genes carried on it. The beginning of the non-homologous region is represented unshaded. This may be either part of the long non-pairing section of X or the short non-pairing section of Y. The cross-over values are calculated from the point where the non-pairing and the pairing regions meet (to = total colour-blindness, X = xeroderma pigmentosum; og = oguchi's disease, ep = recesseive epidermolysrs bullosa; Rp D, and rp = dominant and recessive retinitis pigmentosa). After Haldane.

*Fig. 34*

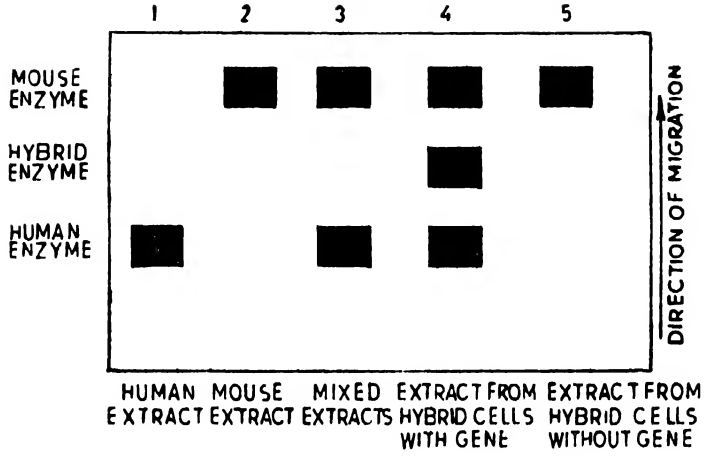
Similar maps of man's other chromosomes or autosomes can only be drawn if we can observe genetic effects which can be directly linked with autosomal genes. Unfortunately, such linkage between phenotype and genotype is riddled with many difficulties in the case of man. It is not merely that we cannot breed men experimentally to produce "pure" lines by brother-sister matings as we can do with animals like banana flies and plants like maize and pea. It is additionally complicated by the extreme variability of the human species due to much larger number of chromosomes of man. As we saw at the outset, the number of possible genotypes that even a

single couple can theoretically produce is astronomical. Consequently, in a species so variable as man, and so largely outbred, scores and even hundreds of differences are being recombined in every family. The clean segregation of single differences such as are observed in simple Mendelian experiments with peas and flies cannot therefore arise. For example, many people have a gene which seems to determine possession of extra *fingers* in their uncles, grandmothers and children but which does not cause them to have the extra *fingers* themselves. It is, therefore, surmised that they carry modifying genes or supergenes which prevent the major gene from asserting itself. The only class of genetical effects in which we can be sure of finding direct and simple Mendelian behaviour is where the genes act directly in producing cell proteins carried in the human red blood cells. Such are the special blood-group genes which prevent the transfusion of blood between genetically different people. It was, therefore, believed that it is *only* by the study of diverse blood group systems to which they give rise that we can gather the information required to make autosomal maps of man. This is no longer the case. Very recently a new technique has been devised to locate human genes on autosomes. It greatly supplements the information provided by the earlier studies of the human blood group systems. We shall dwell on the new technique briefly here before dealing with the blood group systems in the next chapter.

The new technique is an experimental substitute for sexual breeding. As we know, sexual breeding is the fusion of male and female *germ* cells to produce a zygote. In the experimental substitute *body* cells (as opposed to germ cells) from other mammals are fused with those of humans in such a way that the resulting hybrid cells contain different assortments of only a few human chromosomes each. Such somatic (body)-cell hybridization experiments have been performed by taking cells from two species—human fibroblasts (connective tissue cells) and mouse cells. Both these types of cells adapted to tissue culture are mixed in a laboratory dish and allowed to remain in contact for several hours. The contact results in

spontaneous fusion between the rodent and human cells. But as the fused cells obtained are too few to be of much use, the fusion process has to be accelerated by the addition of agents like inactivated Sendai virus which forms intercellular bridges between closely adjacent cells. Having thus obtained sufficient numbers of fused cells, a suspension of highly dispersed parental and fused cells is plated on a culture medium when clones or colonies of cells arise by repeated division of individual parental and fused cells and their progeny. Since the object of the study is the fused cell clones and not its parents, the rodent and human cells, the cells are grown in a selective medium that favours the growth of the fused hybrids but blocks that of the parental cells.

Experiment has shown that fused hybrid cells retain the mouse genome, or genetic materials to which a few human chromosomes are added at random. Thus out of 40 mouse and 46 human chromosomes the fused hybrids consist of 41 to 55 chromosomes instead of the combined total of 86. Of the 41-55 chromosomes forty of mouse are present, the remaining one to fifteen being human. The human chromosomes that the hybrid carries may be of any of the twenty-three in the human genome. For the hybrids that are the result of different fusions carry different human chromosomes at random. Although the hybrid contains only a subset of the full set of 46 human chromosomes tagged on to the full set of 40 mouse chromosomes, both human and mouse chromosomes, in them remain functional. Both types of genes—rodent as well as human—are expressed at the same time each coding for its own specific protein. This dual existence as well as operation does not cause any serious confusion for two reasons. First, the mouse and human chromosomes can be distinguished from one another as also the 23 human chromosomes *inter se* because they differ fairly obviously in shape, size and other ways. They can, therefore, be discriminated by recourse to a refined fluorescent staining technique whereby different chromosomes are shown by their own characteristic patterns of dark and bright bands. The banding patterns serve not only to identify the chromosomes but also provide land-




HOMOLOGOUS ENZYMES are distinguished by electrophoresis. The diagram shows how the process works for glucose -6-phosphate dehydrogenase (G6PD). Cell extracts from each of five sources are placed in channels at base of a starch gel. G6PD is a dimer: a polymer with two subunits. Human cells make a human homopolymer and mouse cells a mouse homopolymer, each of which migrates at a different speed in an electric field, so that the human enzyme (1) does not move as far as the mouse enzyme (2). A mixture of extracts from both kinds of cell shows the two components (3). In a hybrid cell human and mouse subunits are synthesized and interact randomly, giving rise to the two homopolymers and to mouse-human heteropolymers that migrate at an intermediate speed. The enzyme from a hybrid cell that includes the gene for human G6PD therefore separates into three bands (4). Hybrids that do not retain the human G6PD gene produce only the homopolymer from the mouse (5).

Fig. 35

marks along the chromosomal strand. (See Fig. 34). Second, we can likewise distinguish between the operation of mouse and human genes because the enzymes or other protein products to which they give rise can be discriminated. The reason is the great evolutionary distance between mouse and man because of which homologous proteins generally differ in their amino acid makeup. These differences can be detected by another technique known as electrophoresis whereby different enzymes migrate at different speeds in an electric field. (See Fig. 35.) By a conjuction of the staining and electrophoresis techniques we can learn whether two or more genes are on the same chromosome and, if so, to identify the chromosome on which they are located.

The principle underlying the location procedure is simple. It is based on the fact that human chromosomes are usually lost from the hybrid cells as discrete units so that genes that are on the same chromosome are as a rule expressed together. In other words, two genes that are consistently either present together or lost together can be considered to belong to the same chromosome strand. Assaying a number of clones for various enzymes, therefore, provides information whether or not they belong to the same chromosome. Thus if we had 23 rodent human hybrid cell lines, each containing only one human chromosome, and each hybrid retained a different chromosome, the gene for any testable enzyme could be assigned to its proper chromosome. But as in practice it is not possible to obtain such one chromosome hybrid line' a variant of the procedure using eight to ten clone lines has been used to detect the presence or absence of an enzyme and therefore its sponsoring gene in a chromosome. In this way it has been possible to assign some 50 genes to 18 human chromosomes. The aforementioned methods may assign a gene to an individual chromosome but give no indication of its precise location within the chromosome or establish the order in which several genes are arrayed along a chromosomal strand. This further information can often be obtained by making use of chromosomal aberrations such as translocations or deletions which disturb the normal arrangement of genes

within chromosomes. We shall not go into these sophistications except to remark that the loci of some 50 genes, have been discovered by the somatic-cell hybridization technique and its variants.

## CHAPTER VII

# *Heredity and Blood*

BEFORE the discovery of genes and chromosomes around the turn of the century, heredity and blood were by popular consent as closely tied as cause and effect. Heredity was merely a consequence of the passage of "blood"—the blended blood of both parents—to the progeny. The view harks back to Pythagoras who had speculated around 500 B.C. that human life begins with a blend of male and female fluids or semens originating in body parts. Aristotle later postulated that the semens are purified blood, and blood, therefore, is the carrier of heredity. If it happened to be "noble", "royal", "blue", or "pure", the offspring would be brave, beautiful, bright and brilliant. But if it was "common", "base", or "plebian", he would turn out to be criminal, ugly, shifty and depraved. It was this *vox populi* that Thackerey ecohed when he made James Crawley in Vanity Fair say: "Nothing like blood, Sir, in hosses, dawgs and men." We now know better. *Vox populi* that Crawley echoed was not *vox dei* but the voice of ignorance and prejudice. For it is *not* blood that passes from parent to progeny but packets of genes wrapped in chromosomes. Blood is as much the outcome of the chain of biochemical reactions sparked by the inherited genes as any other tissue or organ of the body. Consequently even a mother and her child do not share a single drop of blood

although she carries the fertilized egg during its nine-month long gestation. Indeed, in some cases, she may even unwittingly kill the baby because her blood contains an hereditary "something", the so-called $R_h$ factor, which is hostile to that in her baby's blood as we shall explain more fully later on. It is just as possible for two persons in a family to inherit different kinds of blood as it is for them to inherit differences in eye colour or other physical traits. The reason is that the type of blood an individual inherits is like the colour of his eye or skin wholly genetical regardless of the environment.

It happens that while the choice of eye or skin colour that the genes concerned have is rather limited, that of blood types that the sponsoring genes provide is practically unlimited. The skin colour may be white, black, yellow, brown, mulatto, or copper coloured. But blood types are almost as numerous as the number of possible genotypes. The blood type of an individual may be group B with regard to one factor and group M or MN with regard to another. It may be $R_h$ positive, Kell negative, Duffy positive, and so on with regard to yet other factors. Since each factor gives rise to at least two variations—positive and negative depending on the presence or absence of the factor in question—n factors yield $2^n$ different types of independent blood group systems. Thus, with ten *independent* blood factors there are $2^{10}$ or 1,024 different combinations possible and with an additional ten blood factors the number of combinations swells to $2^{20}$ or 1,048, 576. Considering that 11 independent blood factors are already well established in addition to as many as 70 new factors claimed to have been detected or assumed to exist, the number of combinations possible among general population is inconceivably large. It is so huge that many of these possible combinations like the possible genotypes have not even existed on earth.

The reason for the great variety of blood factors is the fact that although the red blood cells of all normal human beings look alike, they are chemically very different. Each individual's red blood cell carries a set of chemical substances called antigens which vary in type in different individuals and to some extent in different races. It is the discovery of antigens

in red blood cells, that has revealed the extraordinary built-in defence system of the body we now call *immunity* against invasion by foreign microorganisms that continually strive to enter from the outside and infect the body with disease. For we now know that disease and disability may be divided into two categories with only a minor residue that remains indeterminate. There are first conditions which result from the impact of environment on individuals who are otherwise genetically normal. There are, on the other hand, diseases which spring from some genetical abnormality that the individual may inherit. Nearly all diseases and disabilities of the first kind except those which may be caused by malnutrition or physical injury arise from outside infection by harmful bacteria and viruses that somehow enter the body of the individual. It is against such invading microbes that the human body has, during aeons of evolution, built up a natural defence system. For instance, the air we breathe is filtered in the nose where a large portion of microorganisms it contains are caught in mucus and ejected through the nostrils. But besides such purely mechanical barriers the body also resorts to much subtler chemical warfare to destroy or at-least render innocuous those foreign microbes or cells that do somehow manage to enter it. It does so by producing certain substances within the body to make itself immune from the toxins or poisons formed by the invading microbial hosts. If it recovers from the injury inflicted by the invaders, it acquires an immunity from further harm. Such, for instance, is the case with diseases like small-pox, measles, mumps, etc. which are caused by bacteria. A person who has once suffered from these diseases becomes immune to subsequent attacks provided, of course, he survives the first. But the immunity conferred is specific not universal: an attack of measles protects against measles but not against small-pox and vice verse.

The specific immunity that the attack confers may also be acquired by deliberately exposing an individual to a mild infection. This discovery of acquired immunity was made by many early pioneers in immunology, men like Jenner, Pasteur, Kock, von Behring, Ehrlich and others. They showed that immunity against infectious diseases could be induced

in people by active administration of killed or attenuated microbes and their products as effectively as by natural, if more virulent, infection. The methods of prophylactic immunization they devised simply involve imitating natural infection in a controlled manner. There were, of course, many tricks to learn about how to prepare suitable immunizing materials — the vaccines and sera. But they were learnt by empirical means without any knowledge of the immune system at work within our bodies.

Although immunity is still thought of in the context of infectious diseases like small-pox, cholera, diptheria, etc. contemporary immunologists have now moved on from the days of empirical immunization by vaccines and sera to the discovery of the machanism underlying what has turned out to be a highly complex and sophisticated defence system. Theory and practice are at present concerned much more with immune responses against alien cells placed in the body by surgical transplantation or arising in the body as incipient or established cancers. The practical problems that call for solution are to ensure that a kidney transplant is not rejected by the immune response or to accentuate an inadequate immune attack on a malignant tumour. They require a deeper probe into the uncanny capacity of the body to recognize the intrusion of material foreign to itself, be it a virus, bacterium, cell or whatever, and to mobilize cells and cell products to help remove that particular sort of intruder with greater speed and effectiveness. For this purpose two systems of cells have been evolved. In the body they both arise as decendants of stem cells in the bone marrow. They have no immune properties until they have entered and multiplied in an appropriate organ. One such organ is the thymus. There the cells develop and become adapted for their special role as immunocytes of the thymis-dependent or T-series. The other site is not yet known in mammals. It may be somewhere along the intestinal tract from tonsil to appendix, or it may be in the bone marrow itself. These cells become the B-series of immunocytes.

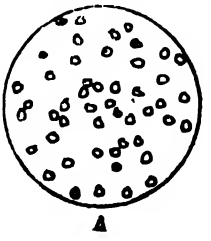
Both B-and T-cells have patches of what it is convenient to call antibody on their surface, and soon after an animal

or baby is born, both series develop a great diversity of antibody patterns but only one pattern per cell. The subject of antibody is far too complex to go into here. Suffice it to say that when a T-cell meets a chemical pattern X, usually on the surface of another cell, it recognizes it instantly because the pattern X and its own immune pattern fit in a complementary manner like a key fitting its lock. Things begin to happen in the wake of such recognition. The T-cell is stimulated to proliferate and produce a family of descendent T-cells all carrying the same immune pattern. When such cells now meet a group of cells carrying pattern X the T-cells attack, and if all goes well, eliminate their target cells. The B-cells have a different approach. Their method of recognizing a foreign pattern in the body is probably basically similar but their response is quite different. They multiply and in the process change to a plasma cell clone. Basically a plasma cell is a highly specialized factory for synthesizing and liberating antibody protein each molecule of which is identical and carries precisely the same pattern as that of the recognition groups on the ancestral B-immunocytes. The antibody has several functions, the most useful of which is brought into play when the foreign pattern is carried by an invasive bacterium. When such an organism is lightly coated, 'opsonized', with antibody it is much more effectively taken in and destroyed by the phagocytic cells of blood and tissues.

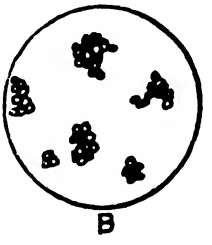
The essential difference between the two systems is that T-cells act *as* cells attaching themselves to and destroying their target cells. Their action is also spoken of as cell-mediated immunity and they are mostly concerned with foreign *cells*. The B-cells are primarily producers of soluble antibody and although antibody can be produced against any form of foreign pattern including those on transplanted or malignant cells, its main value is in protection against bacterial infections.

These principles of immunology govern the genetics of human blood groups. We have already seen how various independent systems of blood groups like OAB, $R_h$, MN, etc. arise because of the presence of certain chemical substances called antigens in red blood cells. It is the presence of anti-

gens in red blood cells that makes them clump together like bunches of grapes, if and when they come in contact with other chemical substances called antibodies carried in the fluid part of the blood, the plasma or serum. See Fig. 36. But




(A) Appearance of red blood cells in normal condition




(B) Appearance of red blood cells when "clumping" in the presence of blood serum containing the associated anti-body

Fig. 36

again this antigen-antibody reaction is highly specific like that of a lock and key. Just as a key will fit only in its own lock, so also an antigen in red blood cells will make them clump together *if and only if* it comes in contact with its *own* associated antibody in the blood plasma and not otherwise. Obviously, therefore, an antigen and its corresponding antibody *cannot* normally coexist in the same individual. It is this property of an antigen to react with its associated antibody that makes indiscriminate blood transfusions so dangerous. For if an individual whose red blood cells carry an antigen such as A were to donate his blood to another, the recipient's blood serum may contain the specific antibody, anti-A, associated with A. If so, the donor's red blood cells

will clump together and block the recipients capillaries often resulting in his death.

We have already described how the antibodies found in blood serum probably arise even though their origin is still something of a mystery. But we now know enough about them to identify them and even to produce them deliberately for use. In fact, their preparation is an essential prelude to the whole process of blood testing exactly as manufacture of reagents of known purity is in chemistry. The first antibodies of this type to be recognised were two which occur naturally and normally in the human blood serum. It was the discovery of these two antibodies and their associated antigens since called A and B by Dr. Karl Landsteiner that is the basis of the "classical" and clinically the most important classification of human blood groups called OAB system. Since there are two antigens A and B, we can have only four mutually exclusive possibilities. Either an individual's red blood cells carry the antigen A (type A), or B (type B), or, both (type AB) or, neither (type O). His blood serum will then contain the antibody corresponding to the antigen he *lacks*, because, as already noted, an antigen and its associated antibody cannot coexist in the same person. Consequently type A will carry in his blood serum the antibody anti-B associated with the antigen B absent in his cells and type B will carry the antibody anti-A. By the same token type AB will carry neither anti-A nor anti-B while type O will carry both anti-A and anti-B. These anti-body-antigen associations are shown in Table 1 below:

Table I

| Blood type of Group | Antigens in red cells | Antibodies in serum |
|---|---|---|
| A | A | anti-B |
| B | B | anti-A |
| AB | A and B | neither |
| O | neither | anti-A and anti-B |

We can now deduce the mutual incompatabilities in blood transfusions of these four groups from the simple fact that

they arise on account of the reaction between the donor's red cells and the recipient's antibodies. Thus, group O maybe given to people of all groups because the donor's red cells have neither antigen A nor B and will not, therefore, react with the antibody in the serum of any of the four groups O, A, B and AB. Likewise, blood group A may be transfused into A and AB recipients and blood group B into B and AB recipients. But blood group A or B may *not* be given to blood group O as the latter's serum contains both anti-A and anti-B antibdies.

Accordingly while group O is compatible with A. B and AB, neither A nor B nor AB is compatible with O. Such compatabilities or incompatabilities between the donor and recipients blood groups are shown in Table 2.

Table 2

| Donor's blood group | Recipient's blood group | | | |
|---|---|---|---|---|
| | O | A | B | AB |
| O | C+ | | C | C |
| A | nC | C | nC | C |
| B | nC | nC | C | C |
| AB | nC | C | nC | C |

It will be observed from the first row and last column of Table 2 that while group O persons are "universal" donors, group AB are "universal" recipients. This is to say that red cells of group O cannot be clumped by any recipient's serum so that their blood may be donated to all blood groups. Per contra, since the serum of group AB cannot clump the red blood cells of any donor, they may receive any type of blood. Such universality as these statements seem to imply is, however, not wholly unqualified. It is limited on two counts.

C+ stands for compatible and nC for non-compatible.

First, the effect of donor's antibodies, if present, is not completely negligible even though it may not be catastrophic. Second, antibodies present in blood serum are of two kinds. They may be "spontaneous", that is to say, they occur naturally in blood serum like the antibodies, anti-A and anti-B, being manufactured in the body without extraneous stimuli. Alternatively, they may arise as "immunity" reaction under some external stimulus in response to the influx of an inappropriate antigen. Such impromptu antibodies are called "immune". For example, there are two such impromptu antibodies, anti-M and anti-N, which are produced in experimental animals by injecting human blood into them. When we do so, the serum of the immunized animal comes to acquire antibodies which can clump human red blood cells. The clumping is due to the existence of their associated antigens in the human red blood cells. For although these "immune" antibodies do not in general occur naturally in human or animal blood sera, their associated antigens M and N do occur "spontaneously" in human red blood cells. The red cells of some persons possess the antigen M; of others N; of still others both M and N. Since antibodies against antigens M and N are not normally present in human blood, MN classification of blood groups is clinically not as significant as the ABO system we have already described.

But it does provide a simpler basis for paternity tests than OAB classification. The reason is that the three genotypes MM, MN, and NN are all phenotypically recognisable. A child who possesses a M or N antigen, not present in the putative parent, cannot be his offspring. However, this test is not able to exclude paternity for a putative father who is MN, since such a man could sire any of the three types of children M, MN or N. Similar tests on the basis of OAB blood groups can, no doubt, be devised. But they are much less conclusive because the inheritance of blood groups OAB is more complex than that of MN group.

Both the blood systems OAB as well as MN are quite independent of each other. Thus a person of blood group, say, B in the OAB system may belong to group M, or, N, or MN in the other. There is no association of any sort linking

the two groups because both groups are the outcome of *separate* sets of genes which segregate according to Mendel's laws as we shall presently show. Consider first the genetics of the MN blood groups. They are due to a single gene having two variants or alleles which we may denote by the symbols M and N. Consequently every individual will have in his appropriate chromosome pair any one of three combinations MM, MN, or NN. But as neither of the two alleles M and N happens to dominate the other, both being equally balanced, or codominant, the three genotypes yield three phenotypes, not two as is the case when one allele happens to dominate its recessive alternative. Those carrying the alleles MM belong to group M, those having NN to group N, and those bearing MN to group MN.

The inheritance of blood groups OAB is a little more complex than that of MN groups or other wholly genetical traits we have so far considered. In these relatively simpler situations every gene had two variants or alleles one of which was dominant over the other or codominant with it. But many genes have mutated more than once in evolution and now exist in three or more different forms. A case in point is the gene responsible for the classical blood groups ABO system. This gene exists in three allele forms A, B and O of which forms A and B are dominant over O but forms A and B are codominant, neither being dominant over the other. Consequently the phenotypes produced by genotypes AA and AO will be alike as also those by genotypes BB and BO. But the phenotypes produced by the remaining two genotypes AB and OO will be different. It therefore follows that there are six genotypes but only four phenotypes as shown in Table 3 below:

**Table 3**

| Genotype | Phenotype or Blood group |
|---|---|
| AA | A |
| AO | A |
| BB | B |
| BO | B |
| AB | AB |
| OO | O |

That MN and OAB blood groups systems are independent and not sex-linked or otherwise associated because of location in the same autosome pair is shown by the independent assortment of two sets of genes sponsoring these systems. Thus, marriages of OM to ABMN spouses should produce four types of children, AM, BM, AMN, and BMN in equal numbers, if the OAB and MN group genes do segregate independently according to Mendel's second law. For the genotype of group O being OO and of group AB being AB, all the gametes of the former parent will carry only O allele and those of the latter allele A or B in equal numbers. The genotypes of the offsprings will, therefore, be AO and BO in equal numbers. In other words, their blood groups will be A and B in equal proportion. Similarly, the genotypes of the M and MN parent will be MM and MN respectively so that the gametes of one will carry only M allele and those of the other either allele M or N in equal numbers. Hence the genotypes of the offsprings will be MM and MN in equal proportion so that half will belong to M group and the other half to MN. If we compound these two independent assortments, we can easily see that $(\frac{1}{2})^2$ or one quarter of the children will be of the four categories AM, BM, BMN and AMN each as actually observed. We may exhibit the above argument in tabular form as in Table 4.

A glance at the Table 4 below will show that there are in all sixteen classifications; four of each type AM, AMN, BM, BMN. In other words, the matings OM X ABMN will produce four groups AM, AMN, BM, BMN in equal proportion.

We can compute in the same way the frequency ratios of offsprings of the diverse phenotypes likely to result from matings of AM X BM, or OMN × AMN or, any other combinations on the assumption of independent segregation of OAB and MN genes. The actual frequencies observed in every case agree with those inferred from the assumption of the independent assortment of their respective genes in accordance with Mendel's second law. Mendel's second law of segregation applies equally to other genes or supergenes which act as a switch in determining several other blood group systems like $R_h$, P, Lutheran, Duffy, Kell, Lewis, and Kidd systems we

Table 4

Gametes from father's genctype OM=OOMM

| Gametes from mother's genotype ABMN | | OM | OM | OM | OM |
|---|---|---|---|---|---|
| | AM | Genotype AOMM Phenotype (AM) | AOMM (AM) | AOMM (AM) | AOMM (AM) |
| | AN | Genotype AOMN Phenotype (AMN) | AOMN (AMN) | AOMN (AMN) | AOMN (AMN) |
| | BM | Genotype BOMM Phenotype (BM) | BOMM (BM) | BOMM (BM) | BOMM (BM) |
| | BN | Genotype BOMN Phenotype (BMN) | BOMN (BMN) | BOMN (BMN) | BOMN (BMN) |

mentioned at the outset. The controlling genes of each system produce the characteristic antigen present in the red blood cells. The inheritance of these groups may be illustrated by that of the Rhesus or $R_h$ blood group system based on the presence (or absence) of an antigen in the human red blood cells. This antigen called $R_h$ was discovered when its associated antibody was produced by injecting rabbits and guinea-pigs with the blood of rhesus monkeys, whence the name. The blood sera of the "immunized" animals are found to contain an antibody which reacts with its associated antigen $R_h$ in the red cells of some though not all human beings. The antigen $R_h$ is produced by a gene which occurs in two allele forms, one dominant $R_h$ and the other recessive ($r_h$). The genotype $R_hR_h$ and $R_h r_h$ will therefore both be $R_h$ positive, that is, their red blood cells will contain the antigen. But the genotype $r_hr_h$ will be $R_h$ negative, that is, their red blood cells will lack it.

The existence of antigen $R_h$ gives rise to a new kind of blood incompatability which is the cause of a characteristic form of anaemia known as *erythroblastosis fetalis* which occurs occasionally in newborn infants. The infants suffering from this

anaemia are usually $R_h$-positive as also are their fathers, but their mothers are $R_h$-negative. The $R_h$-positive foetus developing in the uterus of an $R_h$-negative mother may pass some of its $R_h$ antigen through the placenta and immunize the mother. The immunization in turn gives rise to anti-$R_h$ antibodies in mother's blood stream. These antibodies may, under certain circumstances such as a succession of several $R_h$-positive pregnancies, gain sufficient strength in mother's blood to be transmitted back through the placenta in the foetus and begin to clump its red blood cells. The clumping reaction between antibodies of the mother and the red cells of her unborn child provokes anaemia. This may be serious enough to cause the death of the newborn infant or abortion of the foetus. See Fig. 37.

It seems that $R_h$ incompatability is only one of a wider class of maternal-foetal incompatabilities that do not surface as they lead to the death of the embryo soon after conception and are, therefore, seldom noticed. Apparently, an embryo of blood group A or B with a group O mother has a risk of 10 per cent of dying as an embryo, presumably from antigen-antibody reactions between embryo and mother. On the other hand, in combinations, in which no such incompatabilities exist, the group O embryos, and perhaps the other homozygous types, are found in deficient numbers at birth and therefore must have died as embryos. Altogether, it has been estimated that about 6 per cent of all fertilized eggs die before birth owing to the effects of this single gene locus. If so, the diverse blood group genes (OAB, MN, $R_h$, etc.) responsible for maternal-foetal incompatabilities must account for a major part, perhaps a majority, of all embryonic deaths. The other major contributor to pre-natal mortality, namely, chromosomal aberrations will be dealt with in the next chapter.

Since most pre-natal mortality whether due to maternal-foetal incompatability or chromosomal aberrations is very early, it is not of serious consequence. But when maternal-foetal incompatability is necessarily lethal before birth as in the case of $R_h$ babies, miscarriages do often turn into tragedies especially as many of them could be prevented with a little forethought. There is practically no risk of any anaemia or abortion resulting from $R_h$ incompatability between an $R_h$-negative mother

STAGE I

THE MATING OF AN $R_h$-POSITIVE FATHER AND $R_h$-NEGATIVE MOTHER WITH $R_h$-NEGATIVE BLOOD SHOWN BY THE SYMBOL (-) PRODUCES AN $R_h$-POSITIVE CHILD WITH $R_h$-POSITIVE BLOOD DENOTED BY THE SYMBOL +

STAGE II

SOME OF THE CHILD'S $R_h$-POSITIVE BLOOD SUBSTANCE OR ANTIGEN TRAVELS THROUGH PLACENTA INTO MOTHER'S BLOOD WHICH BEGINS TO PRODUCE THE ASSOCIATED ANTIBODIES TO ATTACK THE HOSTILE SUBSTANCE.

STAGE III

ANTIBODIES FROM MOTHER'S BLOOD STREAM ENTER THE CHILD'S BLOOD STREAM THROUGH PLACENTA AND BEGINS DESTROYING ITS BLOOD CELLS.

Fig. 37

and her child at the *first* pregnancy provided she has not had transfusions with Rh-positive blood prior to child-bearing. For such transfusions will give rise to antibodies in mother's blood

stream and some of them could linger in her blood for years. In such cases there could be antibodies already present in sufficient strength at her very first Rh pregnancy to attack the child. It, therefore, follows that no young woman with Rh-negative blood should be given Rh-positive blood transfusion. Indeed, such blood transfusions should be avoided in all cases for another reason quite apart from their effect on child-bearing. For repeated transfusions of Rh-positive blood in a negative person of either sex may eventually produce serious adverse reactions. Hence even men with Rh-negative blood should not be given Rh-positive blood transfusions.

Although the binary classification of human blood into two categories, Rh-positive and Rh-negative, is adequate for most clinical purposes such as blood transfusions, it is really an oversimplification of a much more intricate state of affairs The intricacy arises because of the greater discriminating power of the blood serum of a mother, who has had an Rh-pregnancy, than sera of rabbits immunized by blood of rhesus monkeys used for testing the blood of other persons to distinguish Rk-positive from Rh-negative. If we avail of such more potent sera of women, who have had Rh or erythroblastotic infants, we find that there is not one Rh antigen but several different ones detected by specific sera. Thus an Rh-negative woman, immunized during pregnancy by her Rh-positive children, may have in her blood serum antibodies that agglutinate not only Rh-positive cells but also cells from few persons known to be Rh-negative. In this way two additional sera have been discovered for distiguishing Rh-positive from Rh-negative. Use of two additional sera besides that of immunized experimental animals containing antibodies anti-Rh' and anti-Rh' permits recognition of a total of 2 x 2 x 2=8 different variations as shown in Table 5.

As will be seen from Table 5 each antiserum divides the blood tested into two groups, one that reacts positively with it and the other that reacts negatively, so that there are in all eight combinations. These arise because the two additional antisera anti-Rh' and anti-Rh" divide Rh-positive or Rh-negative into four subclasses each. There are thus eight categories in the Rh system which would seem to

Table 5

Agglutination reactions of red cells of different persons to three specific antisera anti-Rh, anti-rh' and anti-rh''

| Anti-$R_h$ | Anti-rh' | Anti-rh'' | |
|---|---|---|---|
| + | − | − | $R_h$-positive |
| + | + | − | |
| + | − | + | |
| + | + | + | |
| − | − | − | $R_h$-negative |
| − | + | − | |
| − | − | + | |
| − | + | + | |

suggest the existence of eight variants or alleles of the gene sponsoring the $R_h$ system. The inheritance of these eight $R_h$ alleles follows Mendel's law of single factor transmission. Any one individual may be homozygous for a single allele or heterozygous for two alleles, but a great variety of different multiple alleles may be found in any population.

Although we have considered in some detail only three blood systems—ABO, MN and $R_h$—there are several other blood systems which are known to be inherited independently of each other. Table 6 below lists a few of these systems. Apart from the first namely, P system, all others have been named after the first known carriers of the antibodies or of antigens on which the system is based.

Table 6

| Blood System | Symbols for Alleles |
|---|---|
| P | $P_1$, $P_2$, p |
| Kell | K, k, $k^p$ |
| Lutheran | $L_u{}^a$, $L_u{}^b$ |
| Duffy | $F_y{}^a$ $F_y{}^b$ |
| Kidd | $J_k{}^a$ $J_k{}^b$ |
| Lewis | $L_e$ $l_e$ |

As will be observed, first two systems have three variants or alleles of the sponsoring genes but the remaining four have only two. These alleles either determine the presence or absence of an antigen or a pair of alternative antigens or control more complex situations such as those described for the OAB, MN and $R_h$ systems. Although the clinical applications of the systems sponsored by these genes are for the future to unfold, their study is nevertheless of great theoretical importance in human genetics. For these antigen-producing genes are the few types of human genes whose clean segretation according to Mendel's laws can be directly observed so that it is possible to link phenotype to genotype with some measure of precision as in the case of some of the sex-linked genes. Such genes therefore act as markers on several autosomes and thereby facilitate the observation of linkage and measurement of crossover values required for the genetic mapping of the human autosomes. Indeed, as indicated by Sir Ronald Fisher in his Preface to *Blood Groups in Man*, by R.R. Race and R. Songer, "now that usable marked loci have been established on ten of the twenty-three human autosomes we are at the dawn of the period in which our own chromosomes can be adequately surveyed". Once drawn these autosomal maps will be of great value in mitigating the distress caused by certain unifactorial hereditary diseases which though individually rare together constitute an important problem.

# CHAPTER VIII

# *Heredity and Disease*

WHEN Shakespeare wrote about a "mildewed ear blasting his wholesome brother", he had a clear premonition of what we now call infection. Yet three centuries later, the famous botanist, Professor Lindley, when confronted with the potato blight which brought famine to Ireland in 1846, put the cart before the horse and held that mildew was the consequence and not the cause of the disease. He continued to believe that the diseases of plants were "plainly and directly hereditary". The temptation to attribute the unknown cause of disease whether of plants, animals or men to some still more unknown factor like heredity was the type of *obscurum per obscurius* that was a favourite pastime of the learned scholars at the time. Faced with a multitude of diseases that could not be cured learned men were strongly tempted to believe them to be hereditary. Indeed, many of these diseases must have appeared like tuberculosis to be genetically determined wastage of the human body merely because some families suffered from them more than others. Thanks to our new knowledge of the interplay of heredity and environment we now know better. As we had occasion to point out earlier, there are two types of disease and disability: type I due to the impact of outside infection (environment) on the individual, and type II due to some

genetical abnormality that the individual may inherit. But this binary classification of diseases into environmental and hereditary is an oversimplication of a vastly complicated situation. Even if we leave aside diseases whose causes are still unknown, there are quite a number which are a betwixt and between of environmental and genetical diseases. It, therefore, happens that many types of diseases like schizophrenia and mental conditions arise only if the genetical predelictions one inherits show themselves in an adverse environment. What is even more important is a person's whole genetic makeup—his complete genotype—in relation to almost every disease and, in particular, its virulence. For even when a condition is largely environmental, individuals who differ genetically will react to it in different ways. A strong constitution like that of Casenova or Schopenhauer may live almost up to Palmists' three score and ten despite syphlis while another like Henry VIII or Nietzche may succumb to it in comparative youth. The most striking difference in this respect is that between males and females.

Even though woman is considered the weaker vessel, it is the male who is far more vulnerable to most diseases and defects - almost all except those which are chiefly glandular or which are peculiar to females. The reason for this discrimination seems to lie in the fact that the human female has to bear the burden of maternity. She is therefore genetically more robust, has a more efficient internal chemical system, and in various other ways is biologically better adapted to resist most of the modern human afflictions. One auch advantage is that she starts off with two X chromosomes (one from each parent), while the male gets only one X from his mother, the other chromosome Y from his father is only an atrophied one with very few genes. Accordingly if any lethal or semi-lethal genes are in the male's X chromosome, it is usually far more dangerous for him than it would be for his sister even if she inherited the very same X. For the defective gene being recessive will be suppressed by a normal gene in her other X. The poor male with his atrophied Y has no spare to quell the aberrant gene in his single X. In so far as there are a great many recessive genes in the X chromosome which every so often are defective, males, by and large, are directly exposed at

conception to many more special defects and afflictions than are females. However, defective genes are not necessarily confined to sex chromosomes which make males more liable to certain kinds of hereditary afflictions. They may arise equally on autosomes. When they do, the upshot is a hereditary disease to which both sexes are more or less equally prone. That such defective genes sometimes do occur in chromosomes is not surprising. For, as we have seen, genes act as initiators as well as regulators of the processes of life as they occur within each individual, first in the cells and then in the tissues and organs whose integrated activities constitute the individual. No wonder that among the thousands of genes at work in the development and growth of an individual a few may malfunction and thereby give rise to a hereditary disease.

The malfunctioning genes usually arise by a process called mutation that is, miscarriage of the replication process whereby each gene is able to produce a copy of itself. This replication process by which chromosomes and genes duplicate themselves is remarkably accurate. It results in the production of millions and billions of cells with exactly the same genes. The duplicate genes so produced are quite stable and durable. The reason for their remarkable stability lies in the fact already noted in Chapter V, namely, that they are large micromolecules held together by quantum-mechanical bonds of substantial strength. Nevertheless, once in a rare while something goes wrong. A gene is not exactly the same as the old one, or the order of the genes on the chromosome is altered. The bond forces holding the gene together may also be overcome by exposure of germinal tissue to X-rays, ultraviolet light and a number of other sources of energy. As a result artificial mutations may also be induced. But the effects of these induced mutations are as random in direction as those of spontaneous ones. All these miscarriages of the replication process whether occuring spontaneously or otherwise are called mutations.

When a chromosome on which a mutation has occurred makes a duplicate of itself in preparation for the next cell division, it copies the mutated gene or the new gene arrangement as faithfully as it copies the unaltered portions.

Consequently a mutation once it has occurred is inherited and becomes perpetuated exactly like the original gene from which it arose. Since a normal gene has during the acons of evolution accommodated itself to the intricate process of reproducing and maintaining the host organism, a mutated gene has to seek fresh accommodation with its *milieu interne* as well as *externe*, if it is to prove beneficial. But it is unlikely that a chance mutation will enable the affected gene to regain its disturbed *modus vivendi*. This is why most mutations are injurious and give rise to hereditary diseases in man as well as in plants and animals.

But there do arise once in a while some mutations that are either better or at any rate no worse than their originals. Both are preserved by natural selection. The better ones are the main source of the emergence of higher and newer forms of life we call evolution. The "no-worse" ones give rise to the co-existence of several types of the same species called polymorphism. A case in point is the variety of genes that sponsor diverse blood groups like OAB in human beings. Since there was no evidence that one gene that gave rise to blood group A was any better than its alternative that led to group O, it was widely believed that blood group genes were "neutral" genes. Mankind was said to be polymorphic with respect to these genes. Speaking more precisely polymorphism may be defined as "occurrence together in the same locality of two or more distinct forms of a species in such proportions that the rarest of them cannot be maintained by merely recurrent mutation".

Surprising as it may seem, recent research has shown that "neutral genes" are not that neutral after all. Highly sensitive statistical tests seem to show that a person of blood group A is more likely to suffer from stomach cancer than members of other blood groups B, AB and O. Similarly members of blood group B are more prone to peptic ulcers. The statistical differences are, no doubt, slight but nevertheless significant. But their "significance" is only statistical, that is, actuarial not individual. They, however, do suffice to allow natural selection to exert its pressure.

With the fading out of the "neutral genes" assumption

every polymorphism is now seen as a problem in that certain types that were "no worse" than their forbears at the time of their emergence could become *either* better *or* worse later with changing environment. Unfortunately, we cannot even discover what would happen because of the great complexity of the complimentary relationship between heredity and environment. For example, when a particular variant of the human environment disappears owing to the "march of history or progress" what happens—or what should happen—to the genetic variant best suited to the vanished environment? We simply don't know.

However, we do know in much greater detail the effects of injurious mutations, the main cause of genetic diseases in men, animals and plants. They occur not merely because a mutant gene is unable to function normally. They also arise from purely chromosomal aberrations even when the genes remain unmutated. All such diseases whether due to gene mutations or chromosomal aberrations may be divided into two broad categories: (a) those correlated with visible abnormalities in number and form of chromosomes; and (b) those due to gene mutations. About six per cent of children born alive show recognizable genetic defects of type (a) or (b). Both are serious enough. But type (b) abnormalities due to gene mutations are in general much more vicious even lethal than type (a) due to chromosomal aberrations. The reason seems to be that any gross chromosomal abnormality is incompatible with life. Most chromosomal abnormalities that occur are therefore aborted before birth. The total embryonic death rate due to this factor is unknown as there is no accurate measure of human conceptions. But it may be inferred from the fact that in other animals like cattle, sheep, mice and rabbits prenatal mortality averages some 30 to 40 per cent. It is believed that chromosomal abnormalities are substantial contributors to this death rate. Another major contributor is maternal-foetal incompatability already referred to in Chapter VII.

Despite the incompatability of chromosomal abnormalities with life some children are born with abnormal chromosomal inheritance. Such abnormality is confined only to sex chromo-

somes and one of the smallest autosomes. As we have seen, a normal individual will have a pair of sex chromosomes—XX in the female and XY in the male. But there are several anomalous conditions in which X and Y chromosomes are in abnormal conditions such as XO, XXX, XYY, XXY. A comparison of these patterns with the normal combinations XY or XX will show what might be expected. Thus when Y is absent the resultant individual XO is an apparent female anatomically but remains sexually immature and sterile. An XYY individual with an extra male chromosome Y is usually predisposed to criminal violence. Likewise, an XXY individual with an extra female chromosome X is outwardly a male but has very small testes and somewhat feminized breasts. All these abnormal types have subnormal intelligence. Their abnormalities seem irremediable. No gentic engineering technique has yet been devised to make an XO inter-sex into a normal woman by adding the missing X, or remove the unwanted Y from the criminal supermale XYY or X from the nancy male XXY.

Another chromosomal abnormality that is *not* aborted before birth consists in the individual having 47 chromosomes instead of 46, the additional one being a member of the smallest group of chromosomes. There are three variants of one chromosome (number 21) instead of the normal two. The usual explanation is that during meiosis which reduces the number of chromosomes from 46 to 23 in the female ovum, a mechanical error results in both the small chromosomes in pair number 21 passing to the ovum instead of only one. The upshot is a baby born with Mongolism or Down's syndrome, a type of feeble-mindedness with relatively minor anatomical change seen particularly in children born when their mothers are approaching menopause.

Far more interesting are genetic diseases that arise essentially from the mutation of a single gene allowing a simple Mendelian distribution to appear in the offspring concerned. To fix ideas, suppose we have an affliction-free population of heterozygous individuals of normal genotype (Aa). If the recessive gene (a) suffers a mutation even in a few cases, the mutant individual's genotype will become (Aa') instead of (Aa) even though their phenotype remains unaltered. If now

two individuals of genotype (Aa') happen to mate, one quarter of their children will be double recessive homozygotes a' a'and will therefore show the affliction sponsored by the mutated gene a'. The remaining children having at least one dominant (A) in their genotype will either be normal (AA) or only carriers (Aa') of the deviant gene a'.

We may illustrate this principle by the specific case of a genetic disease called infantile amaurotic idiocy which results in early death of the victim. The parents of amaurotic idiots are normal people blissfully unaware that they are carrying in their genotype the mutated gene a' responsible for the affliction instead of the normal a. They seem normal because they also have the dominant allele A which suppresses the effect of its deviant counterpart a'. But the suppressed deviant shows itselt in their progeny. For one quarter of the children of such parents will be double recessive homozygotes a' a' and will die of the disease. Among the survivors two-thirds will be carriers Aa' and one-third will be normal AA. It is obvious that marriages in which only *one* of the mates is hetrozygote (Aa') run no risk of producing afflicted children though one-half of their progeny will be carriers. Similar is the case with another disease called juvenile amauratic idiocy which is also caused by a mutated recessive gene. Infants homozygous for this (recessive) gene appear normal at birth. But by the time they are four to seven year old, their eyesight begins to fall gradually till they become totally blind. At the same time their mental and physical powers deteriorate leading inexorably to death before or during adolescence.

Both the mutant genes responsible for the aforementioned afflictions are recessive and lethal. as indeed is the case with most other lethal genes. It is not difficult to see why most lethal mutants are recessive. A dominant mutation expresses itself in the first generation that receives it. If it happens to be lethal. dominants will die out immediately after they arise without ever having a chance to accumulate in a population. But a recessive will be carried for many generations by heterozygotes as only homozygotes with a double recessive dose are afflicted. Nevertheless, a noteworthy exception

to this rule is a mutant gene labelled (T) which produces an anamolous variant of haemoglobin in the recipients' blood. Since it is haemoglobin that enables the blood stream to carry oxygen from the lungs to body tissues and cells, the abnormal haemoglobin it produees leads to a species of anaemia. In the homozygous condition TT, the result is a fatal anaemia (Cooley's anaemia). But it is vicious enough even when alone, for in the heterozygotes (Tt) it gives rise to an anaemic condition called thalassemia. This hereditary anaemia was first recognised in the populations of the Mediterranean countries where malaria has been rampant for centuries. The emergence of the aberrant mutant T in malaria-ridden countries is now believed to be an evolutionary counterblast to malaria. For it seems that in a malarial region it is an advantage to have the thalassaemia trait. Infections with malignant tertiary malaria are reported to be less severe in the heterozygotes (Tt) than those with the normal homozygotes (tt). Since the malarial parasite multiplies in the red cell living largely on haemoglobin, it is not surprising that this should be so.

The prevalence of another fatal anaemia known as stickle cell anaemia in the malarial regions of Central Africa seems to support the correlation between malaria and anaemia. Sickle cell anaemia is due to a recessive mutant gene (a) which produces yet another abnormal variant of haemoglobin. This variant can carry only half the normal amount of oxygen from the lungs to the diverse parts of the body. As a result dominant homozygotes (AA) are normal, while recessive homozygotes (aa) die of stickle cell anaemia. The heterozygotes (Aa) are only half anaemic. But the debility has its compensation. It enables the recipient to resist malaria better than the normal homozygotes (AA) and survive. Natural evolution seems to have deliberately distorted human haemoglobin molecules in order to spite the malarial parasite.

The emergence of aberrant mutants like the gene (a) responsible for stickle cell anaemia illustrates Haldane's dictum that resistance to an infectious disease in many cases involves highly specific mechanisms that are of no use in other

contexts and may in fact be harmful. Thus populations living in regions ridden with malaria in the past but now well on the way to freedom from it, thanks to modern sanitation and insecticides, still carry the gene (a) which continues to exact its toll in anaemia without any compensating benefit from malaria resistance. There is the possibility that several genes whose present function is obscure are relics of former disease resistance mechanisms in which they were somehow involved, or were selected for other less obvious reasons that are no longer relevant.

Besides the aforementioned varieties of idiocies and anaemias there are many other forms of imbecility as well as diseases, disorders and abnormalities which are now known to have an hereditary basis. Some of these assert themselves during infancy while many inherited disorders appear in later years They include certain nervous diseases like Hutington's chorea and schizophrenia, defects of the circulatory systems, some kinds of cancers, and many other afflictions of old age. We still do not know precisely what specific malfunctioning of the aberrant gene (a) causes them. But most of them seem to arise because of what Sir Archibald Garrod has called "inborn errors of metabolishm". The errors are "inborn" because the mutant gene is no longer able to control the individual's metabolism as well as its original unmutated counterpart could. For even though the primary function of genes is self-replication, genes are also active in the subsequent synthetic processes of the cell that result in the production of specific metabolites and especially with specific proteins such as the enzymea as we observed in Chapter V. Further proof that specific genes are concerned in the synthesis of specific proteins has been obtained from observations of difference in protein structure in individuals with different alleles of the same gene one of which has arisen by mutation. Such comparisons of effects on metabolic processes of mutant genes with those of their normal alleles has shown that individual genes exercise controlling influence on specific pathways by which metabolites are synthesized or broken down. In microorganisms one step in the synthesis of an essential amino acid such as arginine fails to occur when a specific mutant is

substituted for its normal counterpart. Another step in the same synthesis fails in the presence of another mutant. Many instances of the control of separate sequential steps in a synthesis by separately mutant genes have followed the pattern "p" → "a" → "b" → "c" → "s", in which the conversion of a precurser "p" into a compound "a" fails in the presence of a mutant a, step "a" into "b" fails in the presence of mutant b, and so on. In the presence of a mutant unable to carry out the ultimate step "e" into ' s", the synthesis of the substance "s" fails even though all preceding steps have occurred normally.

Similar metabolic pathways in higher organisms have been shown to be controlled by specific genes. In man, for example, there is a metabolic pathway which converts phenylalanine one of the amino acids essential for human nutrition, into various products, a, b, c, d,...by means of gene mediated chemical reactions in accordance with the principle: one gene, one reaction. The next step 'a' in this conversion happens to be the production of tyrosine. If the mutant gene responsible for it malfunctions, the unassimilated phenylalanine accumulates in the blood and is excreted in lar e quantities in the urine. The upshot is a disease called phenylketonuria (PKU) which results in mental deficiency. For persistence of high concentration of unbroken phenylalanine over the first few years of a PKU baby causes serious brain damage making him a low-grade mental defective. Another interruption in the same metabolic pathway but at a subsequent step such as (s) leads to accumulation of another unassimilated chemical in the urine which makes it black. This disorder is called *alcaptonuria.*

The actual mechanism by which mutant genes block individual steps in metabolic pathways is unknown. But it is believed to be due to the mutant's inability to produce the appropriate enzyme responsible for catalyzing the step that fails. Similarly, by extension, it has been supposed that genes exercise control over metabolism through the production of specific enzymes, each enzyme receiving its specifications from a gene.

Phenylketonuria and alcaptonuria are not the only hereditary diseases that arise from inborn errors of metabolism caused by malfunctioning mutant genes. There are many others that are caused in a similar way, namely, a specific mutant gene initiating a change in the nature of a specific enzyme. Such genetic effects are simply failures to make a specific enzyme necessary for a given metabolic pathway which is synthesized by the normal gene. In the absence of the enzyme, the metabolism of the cells is altered with consequences that may be harmless, injurious or lethal depending on the importance of the biochemical reaction catalyzed by the enzyme in question. For example, a rare mutation in human beings is associated with the loss of an enzyme necessary for the normal degradation of glactose, a constituent of lactose, or milk sugar. This disease, like phenylketonuria, is inherited as a recessive. Children homozygous on this gene cannot digest glactose or milk sugar. For individuals with this mutation, milk is a toxic substance because glactose accumulates in tissues when lactose is ingested. The accumulation of glactose gives rise to a number of clinical effects like enlargement of liver, development of cataracts and loss of weight by the patient. Since lactose is generally absent in foods other than milk, these deleterious effacts of the injurious mutation can be avoided simply by abstention from milk. But the effect of other mutations like PKU seem more difficult to control.

At first sight, it may seem as simple to deal with PKU as with the incapacity to digest milk. All we need do is to feed the infant from birth a diet which has a minimal amount of phenylalanine. There are available digests of milk protein from which most of phenylalanine is chemically removed. If such digests are made the main source of protein, or protein equivalent, in the diet, there is no doubt that a proportion of PKU children develop better than the average untreated case. But treated cases do not seem to escape damage of one sort or another. There is now reason to believe that the level of phenylalanine which can be tolerated in the blood is highly critical. Too much phenylalanine causes brain damage; too little leads to a condition that resembles a protein defiency disease known as kwashiorkor which itself gives rise to brain damage.

What is the right critical level for any individual is hard to determine. If ever one's meat is another's poison, it is the quantitites of phenylalanine that a PKU baby can tolerate.

The only cure therefore would seem to be to synthesize the particular enzyme required to remove the metabolic block. This is the obvious general approach in treating several similar genetically sponsored diseases that was suggested two decades ago when chemists began to synthesize proteins and could optimistically hope to make the needed enzymes. It then seemed as if enzymology, the manufacture of appropriate enzymes, would be the keystone of the arch of medicine and pharmacology. Indeed, the celebrated chemist, Linus Pauling, even predicted that before long when our understanding of enzyme activity has advanced sufficiently, many of these hereditary diseases would be treated by the use of *artificial* enzymes specially synthesized to catalyze the biochemical reactions within the body, which its mutant genes fail to sponsor or support very much as we now-a-days treat diabetes with insulin.But as the insulin used by diabetics at present is pig and beef insulin, it is not free from risk of allergy or antibody reaction. It is the same with the current treatment of haemophilia, caused by the failure of the body to manufacture human blood protein known as factor VIII. Haemophiliacs are therefore treated with factor VIII prepared from concentrates of human blood plasma. Since such concentrates often contain the pooled blood of up to 20,000 blood donors, the factor VIII derived from them is highly susceptible to viral contamination. All such concentrates are infected with hepatitis virus with the result that many haemophiliacs so treated suffer from liver disfunction caused by hepatitis. They are also very prone to acquired immune deficiency syndrome (AIDS) because an AIDS virus can also contaminate factor VIII produced from blood plasma pooled from many donors. The treatment is threfore like jumping from the frying pan, if not, into the fire at least into exceedingly hot water.

Fortunately, as will be seen more fully in Chapter XIII, it seems likely that both the production of insulin as well as factor VIII by recourse to new genetic enginering techniques may yield products free from their present drawbacks. But

treatment of most other genetic diseases in a similar way has as yet no such glimmer of a silver lining to come. This is the case with at least ten usual y fatal genetic diseases like Tay Sach's disease, Fabry's disease, Krabbes' disease, Gaucher's disease, which are caused by inherited enzyme deficiencies. But results of treatment by supplying synthetic enzyme the body fails to provide are far from encouraging. Take, for instance, Tay Sach's disease, which is children's disease caused by excessive accumulation of a certain fatty material (lipid) in the blood stream and tissues of the body leading to muscular weakness and severe progressive mental retardation. Although the missing enzyme required to dissolve the accumulated lipid has recently been synthesized, its injection into an infant with Tay Sach's disease has not been much of a success because the enzyme is not able to cross the blood brain barrier, the mechanism by which the blood vessels of the brain exclude certain substances that interfere with the metabolism of brain cells. The best that can be hoped for at present is the treatment of people with lipid storage diseases that do not affect brain cells. But even such simpler genetic anamolies are not easy to cure. For even if we could establish the structure of the normal enzyme that the mutant gene fails to produce — itself a stupendous feat of enzyme chemistry— its synthesis *in vitro* is only the beginning of real difficulties, which will have to be overcome to get it at the requisite metabolic site in appropriate concentration. Each one of the sequence of steps from fixing the structure of the enzyme in question to its synthesis and delivery at the right place may be possible "in principle". But with the restricted knowledge of the overall chemistry of the human body we have, the practical implementation of what seems possible only "in principle" would repuire an army of first rate scientists and technicians. As Sir Macfarlane Burnet has pointed out, "There could never, in my opinion, be adequate motivation for any government to finance such a research or for any individual scientist to undertake the responsibility for its technical direction". The reason is that many eminent men of medicine are facing a severe moral dilemma. The logic of the present situation confronting them demands that infants with gross genetic defects

of metabolism should be treated as those with no brain (anecephalic monsters) are treated today and not allowed to survive. The Hippocratic oath they have sworn, on the contrary, demands that they "give no deadly drug to any one though it be asked" "nor counsel such". As always, it will take years before Hippocratic tradition gives way to logic and sanity.

# CHAPTER IX

## *Genetics and Cultigens*

ALTHOUGH genetics as a scientific discipline is a recent innovation, practical genetics as an empirical activity for producing food plants and domestic animals, collectively called cultigens, is as ancient as the old Stone Age. Man has not waited for the full comprehension of the extremely complex phenomenon of heredity before formulating provisional laws by which he could attempt to control their breeding. He proceeded to avail of what he has known since remote antiquity, namely, that like begets like, but the likeness of offspring to parents is not as absolute as congruence or identity. The like offsprings, do vary in several ways. Some are much bigger or more useful to man than others. This basic feature of heredity—likeness tinged with fringe variation—has been used for breeding before the dawn of history. As a result practice has long preceded theory in the breeding of animals and cultivation of food crops as in astronomy. There were many successful plant and animal breeders millennia before Mendel discovered his laws of heredity even as there were many astrologers who could empirically predict the time of eclipses long before Newton founded celestial mechanics. For deliberate breeding must have started with the very dawn of agriculture and animal

husbandry. Pedigree horse-breeding, for instance, is known from documents as far back as 4000 B.C A Babylonion tablet more than 6000 years old shows pedigrees of horses and indicates possible inherited traits. Other old carvings show cross pollination of date palms. Indeed, the main methods for transforming species for practical use or for sporting taste had been well established, if only on a purely empirical basis, from the early days of civilization.

These empirical breeding practices have relied on three sources of novelty. A novel character may arise suddenly within a formerly pure-breeding strain by a process we now call mutation. A case in point is the production of a new variety of rabbit called "Rex". It arose when two ordinary rabbits whose anscestors had ordinary hair unexpectedly produced young offsprings with shorter and softer hair than the normal. By breeding them together the new variety Rex was firmly established. Its skins are used for fur coats and collars. In the same way peas with soft, edible pods arose suddenly from the ordinary kind with hard pods.

Secondly, characters may be combined from two different varieties. For example, if we have a black rabbit with the soft Rex fur, and white one with ordinary fur, we can combine these characters by crossing them. In this case the first generation hybrids are neither Rex nor white but some of the second generation combine both characters. This method has been used very extensively in wheat breeding. Thus Saunders in Alberta used it to combine the frost resistance of a Russian wheat with the high yield of an English one.

Thirdly, if we are dealing with a plant such as the apple, which is usually propogated by cutting, every seedling differs from the parent or parents. If you plant a thousand pips, most of them will not bear such good fruits as the parents, but one of the thousand may carry a lucky recombination of genes, and be worth growing. More than a hundred years ago one Mr. Cox, a brewer at Slough, grew a tree from a pip which bore the lovely scented apples called Cox's Orange Pippin. Cuttings from that tree are ripening their fruit in New Zealand and Australia even today.

It will thus be observed that the empirical practices of breeders of cultigens have either relied on the chance emergence of a favourable "sport" like Rex or on combining such characteristics as are single gene effects. Since only a few of their traits of economic worth to man like yield or weight are single gene effects, the vast majority of the best breeds of domestic plants and animals like hybrid corn and Mexican wheat have been produced by much more rough-and-ready empirical methods of trial and error. Genetic theory is not yet sufficiently advanced to take in its stride such complex cases as polygenic traits.

Consider, for the sake of illustration, the problem of a plant breeder interested in combining in a single genotype all the worthwhile genes of corn. Although geneticists have succeeded in preparing detailed chromosomal as well as cytological maps indicating the location of all genes within each of its ten chromosomes, yet mere location of a gene within a chromosome gives no indication of its genetic worth. But even if we succeeded in marking on these maps all the worthwhile genes, the new knowledge will be of little avail in securing the ideal genotype combining them all. For these genes are scattered in several varieties and there is no short-cut genetic engineering device whereby they can be hand-picked and pooled in a single variety. The only way of combining the genes is to mate the varieties and such mating invariably yields astronomical numbers of genotypes like the possible genetical moulds of human beings cited in Chapter V. For, even one gene, say A and its allele a, segregates in four possible ways giving rise to four genotypes: AA, Aa*, aA*, aa. If there are two genes, their segregation alternatives theoretically are $4 \times 4 = 4^2$, with three genes $4 \times 4 \times 4 = 4^3$, and so on for each successive increase in gene numbers. Assuming that there are no more than three growth-promoting genes *per* chromosome in corn so that there are in all 30 such genes in its ten chromosomes, the number of possible genotype alternatives swells to $4^{30}$—an astronomical number in

[1] Although Aa and aA are the same genotype, the combinations are different.

the range of billion billion ($10^{18}$). Consequently if a corn plant were heterozygous for 30 growth promoting genes, we would have to grow $4^{30}=10^{18}$ plants to obtain a plant homozygous for all 30 dominant growth-promoting genes. Assuming one had a corn field large enough to grow $4^{30}$ plants to secure such a plant—about 2000 times the total land surface of the earth —it would be virtually impossible to distinguish it from others that had an equal number of beneficial genes but some of them in association with their recessive allels, that is, in heterozygous condition. A great many genotypes would have similar phenotypes and consequently would be indistinguishable. But even if the ideal genotype arose by a miracle, there would be no means of recognising it amidst myriad others. The right signal would simply be not heard because of the surrounding noise. It is, therefore, no wonder that no individual corn plant combining all growth-promoting genes—the ideal genotype—has been obtained despite great ado about the possibilities of "genetic engineering". Such feats of genetic manipulation like accumulating all worthwhile genes in a single genotype at one stroke as have been suggested by some science fiction writers are, therefore, only self-deluding fantasies. This is why success in breeding still depends on the breeder's ability to distinguish subtle differences between varieties and select superior individuals, exactly as a master chess player selects a few good moves for exploration in depth out of the vast numbers that are possible. Like the master chess player, he might be at a loss to explain the genetic principle that led him to make his selection decisions. But he makes up for his ignorance of genetical theory by great familiarity with the material under investigation.

An experienced breeder will see points in a cow or a rose which a purely theoretical geneticist would miss completely. It takes years to get one's eye trained in and some farmers never do. A few men have a real genius in this direction, for example, Bakewell, a Leicestershire farmer of the eighteenth century, who revolutionized breeding methods of cattle and sheep in Great Britain long before there was any science of genetics. And there is at least one instance of a contemporary practical plant breeder—T.D.

Lysenko who sometimes suceeeded or at least appeared to have succeeded in producing more robust varieties of winter wheat and other plants by actually denying the validity of Mendel's laws of heredity ! We shall hear more of him in Chapter XII.

Nevertheless, while the practical breeder's selection decisions are still largely empirical, theoretical genetics has at last clarified an ancient puzzle of the pragmatic breeder, namely, is inbreeding a blessing or a blight in the production of cultigens ? It has done so by clarifying our understanding of the mode of reproduction of plants and animals and, in particular, of the principles of inbreeding and outbreeding : the twin ways of shuffling genes whereby new genotypes arise.

As is well known, inbreeding is a mating system in which progeny is produced by closely related parents. Outbreeding is production by unrelated parents. There are various degrees of inbreeding and outbreeding. Brother and sister matings are very close inbreeding, first cousin matings less close. Since remote antiquity the view has been held that inbreeding leads to inferior progeny, a view still embodied in the customs and laws forbidding inbreeding in all civilised countries. Their biological justification lies in the fact that the offspring of matings of close relatives are frequently less vigorous than crossbred individuals. But the extent of deterioration of the viability and vigour produced by inbreeding varies widely in different organisms. There are many plants such as oats, peas and beans which are self-fertilised and thus highly inbred. Per contra, there are others like corn where no inbred lines equal crossbred strains in vigour or yield. Laboratory rats have been inbred by full brother and sister matings for many generations without a decline in vigour. In man, marriages of brothers and sisters as practised in some royal families of Egypt and Peru allegedly led to no undesirable results. And yet in small communities, where there is apt to be a good deal of inbreeding, idiot children are born more frequently than in cities. Then again many of the present-day breeds of farm animals were established by resort to inbreeding as also many outstanding herds of swine, cattle and race horses. What then is the influence of inbreeding on the quality of progeny ? The evidence seemed to

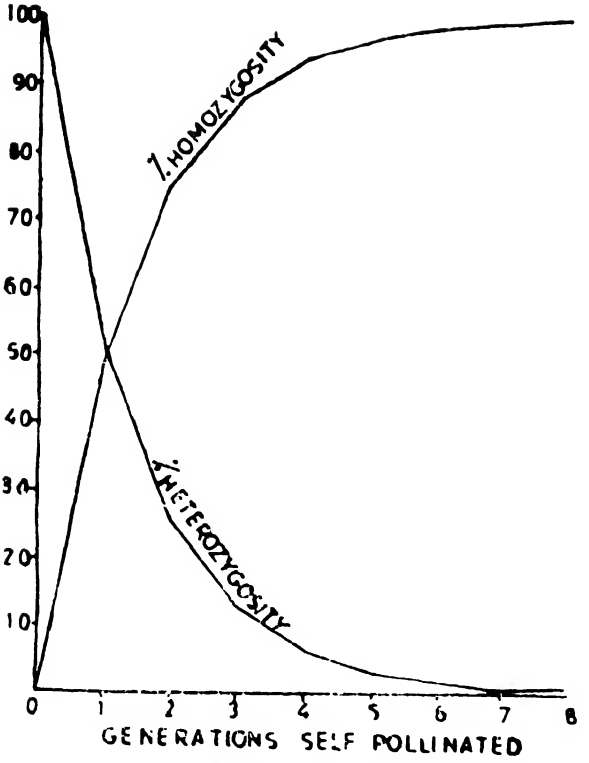
be highly equivocal and great confusion of ideas existed on the subject of inbreeding. It is only after the re-discovery of the Mendelian principles of heredity around the turn of the century that the relative merits and demerits of inbreeding versus outbreeding have been accurately assessed.

It can be shown on the basis of Mendel's laws of heredity that inbreeding tends to eliminate heterozygotes or hybrids from a population and to substitute homozygotes or pure types for them. Thus suppose we have a heterozygous (or hybrid) population of genotype (Aa). As we have seen in Chapter III, their matings will yield offspring in the Mendelian ratio

| | | | | |
|---|---|---|---|---|
| 1 (AA) | : | 2 (Aa) | : | (aa) |
| Dominant homozygote | | Heterozygote or hybrid | | Recessive homozygote |

Thus the upshot of first generation inbreeding is to produce offsprings one half of which are homozygotes (either AA or aa) and the other half hybrid heterozygotes (Aa).

Now the dominant homozygotes (AA) as well as recessives (aa) on inbreeding will only produce their own genotypes (AA) and (aa) respectively. But the heterozygotes (Aa) will produce offspring again in the ratio 1 (AA) : 2 (Aa) : 1 (aa). The second generation of inbreeding halves the population of hybrids once again and so on for each successive generation. After n generations of inbreeding the proportion of hybrids is, therefore, only $1/2^n$. Consequently that of the homozygotes *both* (AA) as well as (aa) is $1-1/2^n$. These proportions may be transformed into percentages by multiplying them by 100. Thus if we started with a population of cent per cent hybrids, their percentage would fall to $100/2 = 50$ per-cent in the first generation, to $100/2^2 = 25$ per-cent in the second, to $100/2^3 = 12.5$ per-cent in the third generation, and so on. After ten generations of inbreeding the percentage of hybrids would be neglibible —only $100/2^{10} = 100/1024 = 0.1$ per-cent—so that for all pratical purposes the hybrids would be eliminated. The population would now consist almost exclusively of the two pure or homozygous classes (AA) and (aa). (See Fig. 38). As a result inbreeding will make the recessive gene




Graph showing the effect of continued self pollination upon homozygosity and heterozygosity.

Fig. 38

(a), whose effect is masked by the presence of the dominant allele (A), in a hybrid, to show itself more and more frequently. If the recessive gene (a) is responsible for an adverse condition like hereditary idiocy, inbreeding will lead to greater frequency of homozygous recessives (aa) having the defective

quality. In such a situation inbreeding is obviously injurious. But if the recessive gene (a) is beneficial or harmless, so will inbreeding be. It, therefore, follows that in a population carrying a rare recessive gene inbreeding is more likely to bring together two such genes and thus to show for good or ill the quality it sponsors. The requirement that the recessive gene under discussion be rare, specified in the preceding statement is important. For, if it was very common in the general population, such as the gene for blue eyes as opposed to brown, any two persons selected at random, but not showing the recesssive, might very well both be hybrids regardless of whether they were related or not In such a case, outbreeding would not necessarily prevent the recessive gene from expressing itself. It is only when a gene is comparatively *rare* in a population that a non-relative of a given hybrid is more likely to be pure dominant than a hybrid. In such cases only will outbreeding prevent the appearance of the trait depending on the recessive gene in question. For, now all the children will receive the dominant from their pure parent. In short, when a recessive gene is *rare* in the general population, inbreeding often allows two such genes to come together and express themselves so that the genetic effect of inbreeding is to breed more homozygous offsprings as against hybrids.

Now many plant species reproduce mostly or exclusively by self-fertilization, which is the closest possible form of inbreeding. Crossing of inbred lines is followed in the immediate offspring by hybrid vigour or heterosis i e., by restoration of the vigour lost during inbreeding. The extent of heterosis is, as expected, proportional to the degree of harmfulness of inbreeding in the same species or race. But this recovery of vigour by outbreeding occurs not because of some peculiar effect that follows upon a mixing of "bloods". Vigour has a definite, though complicated, genetic basis. In plants, it depends on a big system of roots, on well developed leaves with plenty of green colouring substance called chlorophyll, on stout stems, and on many other factors. It is, therefore, no wonder that vigour has a correspondingly complicated genetic basis and is dependent on many genes which are moreover dominant. Let us label only two of these vigour-sponso-

ring dominant genes, A, B, and their weak or recessive counterparts a, b,. If one pure strain has the genotype (AA bb) and another pure strain the genotype (aa BB), then, both will be weak because neither has both the dominants A and B. Suppose we now cross the two strains and produce the hybrid (Aa Bb), the hybrid receives A from one parent and B from another. It also receives the weak genes a and b. But being recessive they do not influence the development of the offspring in the presence of their dominant alleles A and B. This is why the hybrid develops into a plant that is stronger than either parent. This increased vigour produced by crossing two different strains or races is precisely what we earlier called heterosis.

However, if we crossed a strain (AA BB) having both the dominant genes with another, like (aa bb) lacking both, the hybrid (Aa Bb) will not be any stronger than the parent with the dominants. The offsprings are stronger than both parents only when they have more kinds of dominant genes than either parent, as when parents are (AA bb) and (aa BB) and the offspring (Aa Bb). Hybrid vigour is, therefore, not due to hybridity *per se*. It arises only if the hybrid happens to contain more dominant alleles for vigour than either parent. The genetical basis of heterosis is, therefo. , the existence of weak recessives in the hybrid's parents.

Now the reason why weak or deleterious recessive genes accu nulate in natural populations of organisms is the occurence of mutations. In most cases such mutations are known to be unfavourable to their carriers. Unfavourable dominant and semidominant mutants are rapidly eliminated by natural selection. The fate of the unfavourable recessives, however, depends upon the reprodu tive biology of the organism in question. Where self-fertilization or mating of close relatives, that is, inbreeding is the rule as in wheat and many other plants, the recessive defects become homozygous and are eliminated soon after their appearance by natural selection. In such organisms inbreeding is not deleterious simply because the inbreeding process has made them so pure that further inbreeding can have no effect on their vigour. Outbreeding in such cases is not accompanied by heterosis. For

the same reason the various highly selected races of horses and other domesticated animals are not so very adversely affected by inbreeding. They, too, have become comparatively pure by the very process of inbreeding. Since these races, possess a highly selected lot of genes, the only effect of breeding to outside races would be an unfavourable one, from the standpoint of the breeder. In other cases, however, where consanguineous matings are rare and outbreeding is *á la mode*, unfavourable recessives are protected or "sheltered" from natural selection by their dominant alleles, and, therefore, allowed to accumulate in the population. In such cases inbreeding is injurious as it brings together the "sheltered" recessives and thereby allows the recessives to show themselves.

We thus observe that both inbreeding and outbreeding by themselves have an advantage and a disadvantage depending on circumstances. As a rule inbreeding increases "pure lines", outbreeding "hybrids". But inbreeding does not allow for the introduction of benign mutations from outside strains. This is specially true if inbreeding is continued generation after generation. It, therefore, follows that breeders of cultigens have to rely on a judicious blend of inbreeding and outbreeding In this way recessive mutations can come under the influenc eof natural selection (by means of inbreeding) and at the same time beneficial mutations can, from time to time, be introduced into a strain from the outside (by outbreeding). In short, it is by means of selection from inbred or 'pure lines" as well as from hybrids after hybridization that the breeder can bring genes together into all conceivable combinations suitable to the need and fancy of man.

Consider first pure line or inbred selection which was greatly in vogue during the early 1900's for the improvement of naturally self-fertilized species like wheat, oats, barley, cotton, beans and tomotoes. It consists in selecting several superior looking varieties from a large number of genetically different land varieties. Progenies of individual plant selections are then grown and evaluated by simple observation frequently over a period of several years. Later when selections can no longer be made on the basis of simple observation

alone extensive trials are undertaken involving careful measurements to establish real superiority of varieties selected. It is in this way that most of the older varieties of the aforementioned plants actually arose. But a stage comes when further selection on these lines brings dinimishing returns. It then becomes necessary to resort to planned hybridization of carefully selected pure lines or inbred parents to secure further improvement. The object of hybridization is to combine desirable genes found in two or more different varieties to produce pure-breeding progeny superior in many respects to parental varieties. The main difficulty is the proliferation of possible genotypes that occurs in generations following hybridization. We observed how large number of corn genotypes arise even when we try to keep track of only 30 growth promoting genes. One simply cannot do without efficient techniques in managing huge numbers of hybrid genotypes that can arise. There are two widely used techniques to keep in check proliferation of genotypes. One is called pedigree procedure and the other bulk breeding method.

Pedigree breeding starts with the crossing of two genotypes, each of which has one or more desirable characters lacked by the other. If the two original parents do not provide all of the desired characters, a third parent can be included by crossing it to one of the hybrid progeny of the first generation ($F_1$). Superior types are then selected in successive generations, and a record is maintained of parent-progent relationships The $F_2$ generation (progeny of the crossing of two $F_1$, individuals) affords the first opportunity for selection in pedigree programme. In this generation the emphasis is on the elimination of individuals carrying undesirable major genes. In the succeeding generations the hybrid gives way to pure-breeding as a result of natural self-pollination, and families derived from different $F_2$ plants begin to display their unique character. Usually one or two superior plants are selected within each superior family in these generations. By the $F_5$ generation the pure breeding condition (homozygosity) si extensive, and emphasis shifts almost entirely to selection between families. The pedigree record is useful in making these eliminations. At this stage each selected family is usually

harvested in mass to obtain the larger amounts of seed needed to evaluate families for quantitative characters. This evaluation is usually carried out in plots sown under conditions that simulate commercial planting practice, as closely as possible. When the number of families has been reduced to manageable proportions by visual selection, usually by $F_7$ or $F_8$ generation, precise evaluation for performance and quality begins. The final evaluation of promising strains involves the following three steps: (a) observation, usually in a number of years and locations to detect weaknesses that may not have appeared previously, (b) precise yield testing, and (c) quality testing. Many breeders test for five years at five representative locations before releasing a new variety for commercial production.

Bulk breeding method differs from the pedigree method primarily in the handling of generations following hybridization. The $F_2$ generation is sown at normal commercial planting rates in a large plot. At maturity the crop is harvested in mass, and the seeds are used to establish the next generation in a similar plot. No record of ancestry is kept. During the period of bulk propagation natural selection tends to eliminate plants having poor survival value. Two types of artificial selections are also often applied: (1) destruction of plants that carry undesirable major genes and (2) mass techniques such as harvesting when only part of the seeds are mature to select for early maturing plants or the use of screens to select for increased seed size. Single plant selections are then made and evaluated in the same way as in the pedigree method. The chief advantage of the bulk population method is that it allows the breeder to handle large numbers of individuals inexpensively.

Often an outstanding variety can be further improved by transferring to it some specific character that it lacks. This can be accomplished by backcross technique described in Chapter III. It consists in first crossing a plant of the superior variety to a plant of donor variety, which carries the trait in question, and then mating the progeny back to a plant having the genotype of the superior variety. After five or six backcrosses the progeny will be hybrid for the character being transferred but like the superior parent for all other genes.

Selfing the last backcross generation, coupled with selection, will give some progeny pure-breeding for the genes being transferred. The advantages of the backcross method are its rapidity, the small number of plants required, and the predictibility of the outcome. Because of these advantages it has been used widely to improve wheat, barley, oats, beans, flax, alfalfa and other crops.

There are, however, cases where "pure-lines" remain much inferior to hybrid varieties no matter how closely inbred. Corn is a case in point. It is an open pollinated and consequently extremely heterozygous. There were no pure lines till their production by G.F. Shull in 1908. He succeeded in obtaining pure lines of corn by self-pollinating or "selfing". But he observed that the self-pollinated lines of corn decreased in vigour with successive generations of selfing or inbreeding as shown in Fig. 39. By crossing different lines Shull was able to produce strains more vigorous than the parent inbred lines. The suggestion was further modified by Donald F. Jones in 1917. The modification, called the double cross, consisted in making a hybrid between two different unrelated single

**Decrease in vigour upon inbreeding**
**Fig. 39**

crosses. Thus suppose inbred lines A and B produce a single cross AB while two other inbred lines C and D yield the cross CD. The hybrid between AB and CD gives a double cross, which combines in one hybrid the gene combinations from four separate inbred lines as shown in Fig. 40.

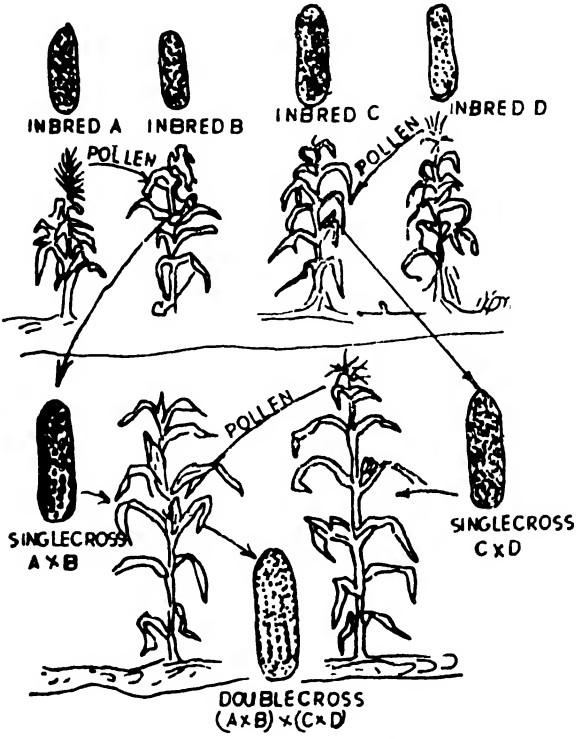


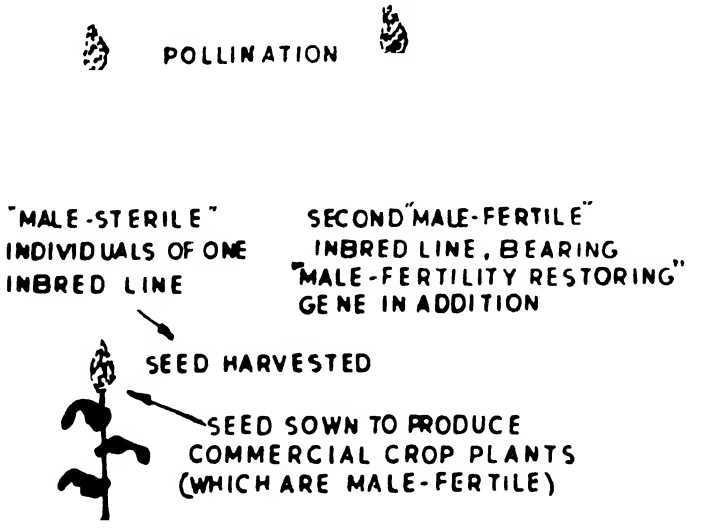

Diagram of method for producing double cross

Fig. 40

Such hybridization has not only vastly increased the yield per acre of the hybrid but also given it many other desirable traits like disease resistance, climatic adaptation, good quality for specific use, etc. No wonder hybrid corn has revolutionized agriculture in the American corn belt and is now on its way to doing so in the rest of world. The price of this progress is increasing specialization in the production of hybrid seed. For the farmer must buy new hybrid seed each year from a

specialised seed producer. There is now in U.S.A. a large, highly organised industry supplying hybrid seed tailored to the climatic, soil, and disease conditions prevailing in the area where the crop will be grown.

The techniques developed for producing hybrid corn are now spreading to the production of other economically important crops also. Thus several varieties of hybrid sorghum and many hybrid onions as well as sugar beets are now being grown. Even hybrid chickens have been produced by first generating certain inbred lines followed by their crossing to yield an extra-quick growing and uniform bird. In sorghum, onions, beets, and now in corn, the hybrids are produced by the "male-sterility" method. For each species, races have been developed containing a gene that causes a failure of pollen production. These races, if grown in the presence of a normal, pollen-fertile race, set their seed by cross-pollination from the latter race. See Fig. 41. In the cases of sorghum and corn, where the seed of the next generation is the desired crop, it is arranged that the pollen from the pollen-fertile parent also carries a "fertility-restoring" gene so that the hybrid plants,




Theoretical basis of the "male sterility" method of producing hybrid sorghum and other crops.

Fig. 41

when they are grown, are capable of forming pollen for the production of their own seed. So successful has this male-sterility method of producing hybrid crops become that the technique is also being used experimentally in the production of "hybrid wheat" even though wheat is a highly inbred crop.

In sum, it is by means of selection of inbred lines and/or their hybridization that the breeder can bring genes together into all conceivable combinations suitable to his purposes. The hybridization of inbred lines may take many forms of which the main ones are the following three.

1. Single Cross $A \times B - AB$
2. Three Way Cross $(A \times B) \times C = (AB)\,C$
3. Double Way Cross $(A \times B) \times (C \times D) = (AB)\,(CD)$

where A,B,C,D represent inbred or pure lines.

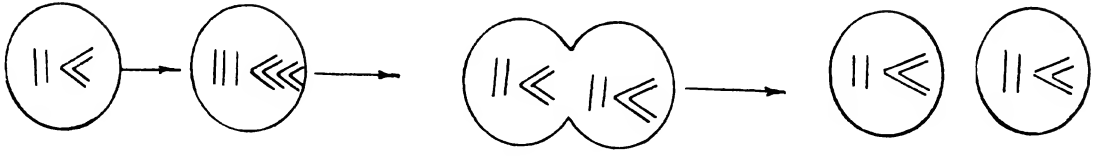
By recourse to one or more of the aforementioned techniques practical breeders have accomplished truly amazing feats like cows that produce over half a ton of butter-fat per year, hens that lay an egg a day, sweet peas and roses of exceeding beauty and bewildering variety, giant dogs for hunting big game or little dwarfs for ladies to hold in their laps, horses that do half a mile in less than a minute or that move a heavy load almost through sheer bulk. But they have produced them after prolonged and patient work extending over many years. There is as yet no royal shortcut to "gentic engineering" in the production of cultigens.

# CHAPTER X

## *Genetics and Cultigens (Contd)*

ONE paradoxical consequence of the immense complexities of the phenomenon of life is that there is no biological generalization or law without its exceptions. It is these exceptions that are often the source of new discoveries in biology. This is why the English geneticist, William Bateson, admonished: "Treasure your exceptions". One such treasureworthy exception pertains to the basic law of heredity requiring chromosomes to occur in pairs within the nucleus of a somatic cell. As we observed in Chapter I, when a normal cell divides into two daughter cells by mitosis, each chromosome duplicates itself just prior to division. Having duplicated themselves the old chromosomes separate from their newly formed duplicates and move to opposite poles when the parent cell is about to divide into two. Both daughter cells thus receive exactly the same numbers and types of chromosomes as the parent has. But it sometimes happens that cell division fails to occur *after* the chromosomes have duplicated themselves. In such a contingency the cell will stay put with *four* chromosomes of each kind instead of only two. In other words, the diploid cell whose nucleus contains a pair of each chromosome becomes a supercell with a set of four chromosomes of each kind instead of becoming two normal diploid cells. See Fig. 42. Such a supercell is

(a)



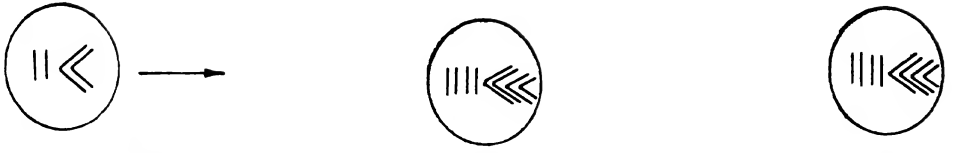
1. ORIGINAL CELL (ONLY TWO PAIRS OF HOMOLOGOUS CHROMOSOMES SHOWN FOR SIMPLIFICATION)

2. EACH CHROMOSOME SPLITS IN HALF LENGTH WISE

3. THE HALVED CHROMOSOMES GO TO OPPOSITE SIDES AND A WALL FORMS BETWEEN THEM AS CELL BEGINS TO DEVIDE

4. THE HALVED CHROMOSOMES GROW TO FULL SIZE RESULTING IN TWO CELLS EACH REPLICA OF THE ORIGINAL

(b)



1. ORIGINAL CELL, ONLY TWO PAIRS OF HOMOLOGOUS CHROMOSOMES SHOWN FOR SIMPLIFICATION

2. EACH CHROMOSOME SPLITS IN HALF LENGTHWISE.

3. THE CELL DIVISION IS HALTED AND THE DIPLOID CELL BECOMES A TETRAPLOID SUPER CELL HAVING FOUR HOMOLOGOUS CHROMOSOMES OF EACH TYPE INSTEAD OF ONLY TWO.

Fig. 42

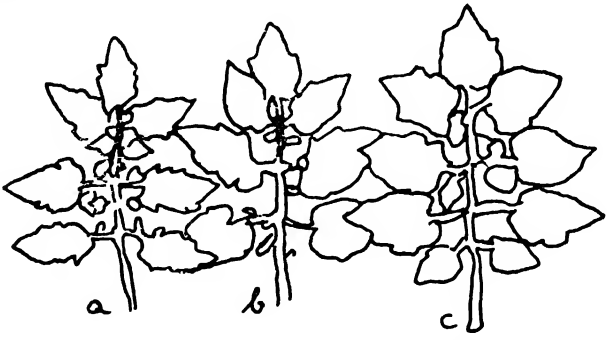
known as tetraploid (or 4n) in contrast to the normal diploid (or 2n). Thus a tetraploid cell might arise as the result of thwarted division, that is, chromosomes duplicate but *not* followed immediately by cell division. Now a tetraploid cell, after a period of rest, might start to divide again. If so, it will give rise to two daughter cells each having a set of four chromosomes of each kind exactly as in the parent cell. Further cell divisions of daughther cells might result in a large number of cells of similar character. For, once the chromosome number has accidently doubled, it remains double from one cell division to the next.

Suppose, now, that the chromosome number has been doubled in a cell of a growing plant and this cell by further division has given rise to a flower. All the unreduced cells in the flower would thus be tetraploid. Before the flower formed its gametes, the reduction division (meiosis) would occur as usual. But as the cell has four chromosomes of each kind, the gametes would contain a double set of chromosomes (diploid number) instead of a single set (the haploid number). If the flower in question were now self-fertilised, two diploid gametes would combine and form a fertilised egg. Since this would contain four chromosomes of each kind (two from each gamete), it would develop into a tetraploid plant. From this a tetraploid race might arise. Now just as a doubling of the chromosome number in bud of a diploid plant (2n) yields a tetraploid (4 n), so a similar doubling in a bud of a tetraploid plant might result in a cell with eight sets of chromosomes (or 8 n) giving rise to an (8n) octaploid race. A further doubling might produce a 16n race, but 16 is about the limit to the number of sets possible in a cell.

Besides doubling of chromosomes due to halted cell division there are other ways in which cells with more than two chromosomes of each kind might arise. Thus a normal diploid plant might cross with a tetraploid. In this event a (1 n) gamete (from the diploid) would combine with a (2n) gamete (from the tetraploid) and the offspring would be a (3n) triploid. A 6 N or hexaploid race might now arise from a doubling in the triploid (3n) plant, or alternatively by the combination of a 2n gamete (from 4n race) and a 4n gamete

from an (8n race). In this way races of plants with various numbers like 3, 4, 6, 8,... sets of chromosomes of each kind might come into existence. All such plants with more than two sets of chromosomes in their cells are known as polyploids.

Polyploids are seldom found in the animal kingdom; but they are not at all uncommon in the plant kingdom. Many cultivated plants like wheat, oats, apples, pears, plums, cherries, strawberries, tomatoes, raspberries, roses, dahlias, etc., are polypoids. Consider, for example, wheat. The basic variety is a diploid plant with seven pairs of chromosomes—a total of 14. There is also a tetraploid with 28 chromosomes. It probably originated from the basic diploid (2n) variety by doubling of the chromosome number. Ordinary wheat is even a higher polyploid. It is hexaploid (6n) with 42 chromosomes. Similarly there are two varieties of tomatoes besides the normal diploid plant. One is a triploid and the other a tetraploid. Fig. 43 shows a triploid and tetraploid tomato plant in juxtaposition with a normal diploid plant by way of comparison.




Typical leaves of diploid (a) triploid (b), and tetraploid (c) tomato plants. (From Jergensen in *The Journal of Genetics.*)

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Polyploidy in plants has two effects: (a) it may result in an increase in size and vigour and (b) it tends to reduce fertility. The increase in size and vigour is by no means universal although polyploid cells are usually larger than their diploid analogues. But polyploids are invariably less fertile. Thus

While triploids are always sterile, tetraploids and hexaploids are not as fertile as their deploid relatives. The reason for triploids' infertility is easily understood. Having an odd number (3) of chromosomes in the nucleus of the cell the gametes formed by cell reduction cannot have equal number of chromosomes. Consequently the gametes, even if formed, cannot fuse so that the plant remains sterile. However, sterility can be an advantage or disadvantage according to the nature of the crop and the method of propagation. Edible fruits may be better without seeds as, for example, the banana, of which common varieties are triploid. Again, among ornamental plants, failure to set seed may lead to a prolongation of flowering. But with grain crops like wheat it is obvious that no reduction in seed setting, that is, fertility, could be tolerated.

Although natural polyploids arise spontaneously, they may also be produced artificially by expert manipulation with a variety of external agents such as Colchicine. Colchicine, by the way, is an age-old drug used to treat gout since the time of Pharoahs. In early 1937, O.J. Eigsti employed it for the first time to induce chromosome doubling artificially. His production of artificial polyploids by recourse to colchicine sparked the hope that artificial or induced polyploidy was an open sesame to vastly improved plant breeding. Unfortunately the hope has not materialised; but what appeared to be a great mystery to earlier plant breeders has been clarified. For, prior to our present understanding of the main facts of polyploidy and, in particular, of the significance of chromosome numbers in plan breeding, the accidental improvements of such partially polyploid crops as irises, orchids, and narcissuses was a great enigma. Plant breeders of these ornamental crops simply tried to replace the smaller diploid varieties of a century ago by the larger flowering tetraploids, triploids, and polyploids when they arose by chance. Unaware of the facts of polyploidy, they did not know how to interpret the differences in breeding behaviour between closely related triploids, tetraploids and polyploids. The development of rapid methods of determining chromosome numbers and the consequent clarification of various

breeding problems relating to polyploidy has, no doubt, unraveled the mystery. But there is now a more sober assessment of the role of polyploidy in plant breeding. It is now realised that despite the major part played by polyploidy in the *natural* evolution of a number of our most important crop plants such as wheat, oats, cotton, tobacco, coffee, etc., artificial polyploidy is no panacea for the plant breeder.

Although colchicine has recently been employed to yield a new polyploid cereal called "triticale" by hybridization of wheat and rye (of which more later), most of the newly produced artificial polyploids were found to be genetically unbalanced and therefore quite inferior. Among the hundreds of polyploids induced in the wake of Eigsti's discovery, only a few survived to remain still in use. That most polyploids like most mutants, whether artificial or natural, are harmful regressions is a consequence of the tragic fact of our life—that of all the myriad ways in which things can happen, only a microscopic fraction of them are favourable to us. It is like the draw of a lottery ticket in your favour. There are a million odd ways in which a lottery ticket may be drawn. But, of these, there is one and only one in your favour. No wonder you have not drawn it yet! It is the same with animals and plants. There are "in principle" millions of ways of changing their genotypes. But even if we could bring these "in principle" ways of genetic manipulation into practice--a brobdingnagian "if"—very few are likely to improve the species. The number of favourable manipulations of the many possible are so few that they can hardly come to pass with our present, rather crude hit-and-miss methods of altering a cultigen's heredity. It was, therefore, inevitable that "Colchicine fad" initiated by Eigsti's discovery should peter out in a few years. The fundamental entropy of change and mutation was once again amply demonstrated by the fact that colchicine and other polyploidy inducing substances used indiscriminately are more likely to produce inferior plants thereby eroding the earlier hope of the emergence of vastly superior crops by recourse to artificial polyploidy.

However, while polyploidy has rarely produced successful types by itself, in conjunction with hybridization it has yielded several superior varieties. Indeed, one of the principal reasons for the success of polyploids in nature appears to be their ability to acquire new gene combinations by hybridization and introgression form a variety of related species. This is precisely how the present varieties of ordinary wheat have arisen. As we mentioned before, ordinary wheat is a hexaploid with 42 chromosomes. The 42-chromosome wheats, the hexaploids, consist of five species which are the most recently evolved of the wheats and are the most useful today, being the bread wheats. All of them are products of the hybridization of 28-chromosome wheats with a diploid wild grass followed by doubling of the chromosome number. The hybridization in question was not deliberately made by man. It occurred naturally because the wild grass which has now been identified as another species of the genus *Aegilops Ae Squarrosa* is a useless weed grass growing in wheat fields, ranging from the Balkans to Afghanistan. Consequently, it would have been present in tetraploid wheat fields of Asia Minor, in a good position to hybridize with the cultivated 28-chromosome wheat plant and produce by natural polyploidy a new kind of hexaploid wheat. Once produced it was selected by man for extensive cultivation for its obvious advantages over its tetraploid counterpart. This emergence of bread wheat occured naturally. Man, no doubt, played a part in bringing wheat parents, the tetraploid plant and the weed grass into accidental contact. But natural hybridization and polyploidy made the next steps. Man simply selected the product.

Although man played only the role of a selector in the establishment of the hexaploid wheat as a grain crop, geneticists have begun to play an increasingly vital role in breeding new varieties since the emergence of genetics as a scientific discipline around the turn of the century. In Europe and the U.S.A., the earlier programmes of deliberate breeding were concerned with artificial hybridization and selection in order to bring together the most desirable characteristics of the

existing strains, thereby combining good milling quality with strong stems and high yield. Now that wheat yields are high and the quality is good, it is more important to produce disease-resistant strains of wheat particularly strains with resistance to stem rust. Stem rust is due to the action of a fungus, *Puccinia graminis*, which is very widespread and very adaptable. It is probably the greatest cause of loss to wheat growers, except for unexpected unfavourable climatic conditions like droughts and floods. The value of such a breeding programme is strikingly illustrated by the success of the effort sponsored by the Rockefeller Foundation and the Mexican government to increase wheat production in Mexico. In 1943, when the programme began Mexico imported half of the wheat consumed in the country. Now, on the average each person consumes twice as much wheat as he did, even though the population has increased by 20 million and Mexico exports wheat! This has been accomplished by concentrating first on the development of resistance to stem-rust disease (including the use of stem-rust resistance races of wheat developed in Kenya), and then by developing high yields through the utilisation of crosses between Mexican races and dwarf races developed in eastern Washington after being produced in Japan.

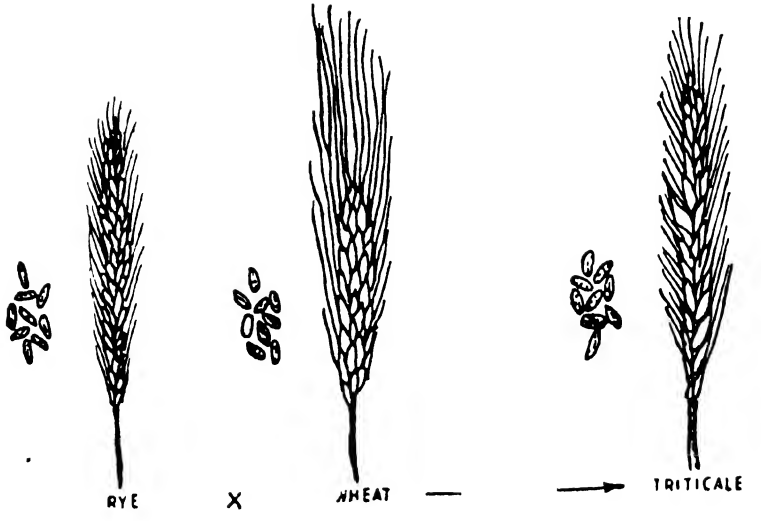
The dwarf varieties had to be developed because wheat plants grown in irrigated soils requiring fertilisers as in Mexico tend to be tall. If a wheat plant has a tall but rather weak stem, it is liable to be beaten down and tangled with its neighbours during rain or in a high wind. This entanglement with neighbours is known as "lodging". But increase in height of the stems is a natural reaction of plants which are given irrigation, water and fertilisers. As water-cum-fertiliser treatment is necessary for high yield of grain, the answer is a dwarf variety. For if an initially dwarf race of wheat can be used, the increase in height produced by the water and fertilizers does not lead to excessive "lodging". The dwarfs also produce more grain per plant, partly because there are more stems and partly because each stem bears more flowers. It is this Mexican dwarf that is the backbone of the Green Revolution inaugurated by the Rockefeller and Mexican wheat

men led by Norman E. Borlaugh, who was awared in 1970 Nobel Peace prize for his outstanding research on high yielding wheat varieties.

However, wheat production in many parts of the world including subtropical and tropical highlands is still limited by stem-rust. Moreover, wheat is not adaptable to adverse environmental conditions such as cold weather and soils that are light, sandy or acidic as rye is. If one could combine the high yield of wheat with the ruggedness of rye, the new blend cereal could be more advantageous than both. This is precisely what the Mexican wheat breeders under Borlaugh in collaboration with the University of Minosota have been endeavouring to evolve during the past fifteen years. They have now succeeded in artifically crossing wheat with rye by cashing on the fact that the basic genome or, genetic material, in both wheat and rye happens to consist of seven chromosomes. For cultivated rye, like the basic variety of wheat, is a diploid plant having seven pairs of chromosomes a total of 14 in all. If a tetraploid wheat with 28 chromosomes is crossed with the diploid rye, the result is a hexaploid plant with 42 chromosomes. But if a hexaploid wheat with 42 chromosomes is crossed with it, the uphot is an octaploid having 56 chromosomes. So far the hexaploid plants have proved to be more stable than the octaploids.

Such crosses of wheat with rye were first attempted as early as 1876 ; but the resultant hybrid plants were found to be totally sterile. They were sterile because the hybrid arose by the combination of a haploid (1n) gamete from the diploid rye and a diploid (2n) gamete from the tetraploid wheat producing a (3n) triploid. And as we have already observed, a triploid plant is always sterile. After Eigstis' discovery of colchicine treatment in 1937, this sterility was no longer an insurmountable obstacle. It was finally overcome by doubling the chramosomes by applying colchicine to the triploid seedling. As a result, the set of chromosomes becomes double yielding the hexaploid plant which is fertile. See Fig. 44.

But colchicine treatment by itself does not suffice. It is necessary to "culture" the embryo suitably prior to colchicine application. This is done by removing the embryo from the

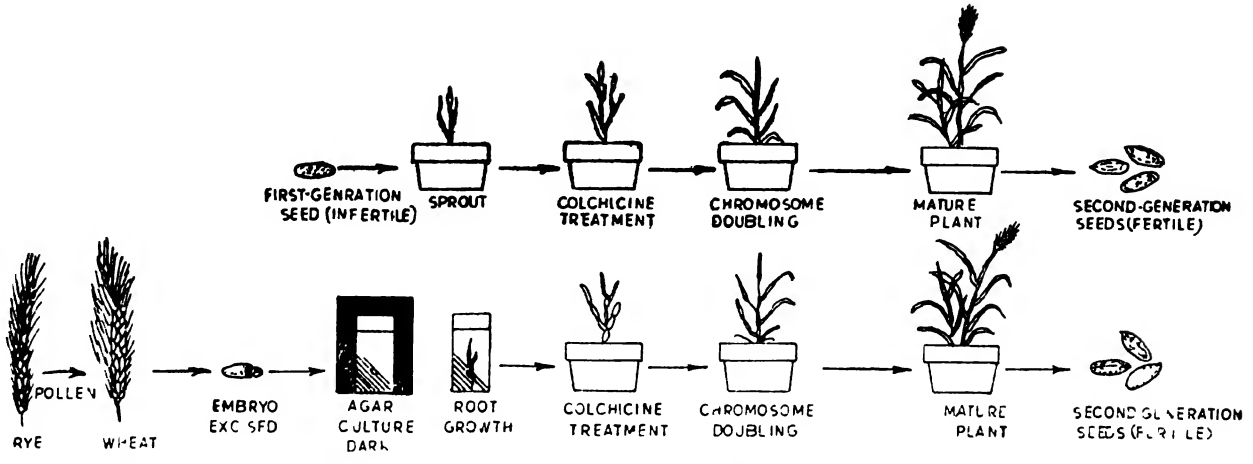



HYBRID IS CREATED by crossbreeding wheat (genus *Triticum*) and rye (genus *Secale*). Tritical is a new genus, and many varieties of it with widely different characteristics can be produced. The crossing is accomplished by transferring pollen from a rye flower (the male parent) to the stigmata of a wheat flower (the female parent). The pollen-carrying parts of the wheat flower are first removed in order to prevent self-fertilization. Grains of triticale generally are larger than wheat grains and plumper than rye grains.

Fig. 44

seed between 10 to 21 days after pollination and transferring it to an agar gel containing inorganic 'salts, other nutrients and sometimes plant growth hormones. The cultured embroy is kept in the dark until roots begin to appear. It is then allowed to grow in light under constant illunination. When shoots have developed the plant is potted in soil. After the hybrid plant has produced several shoots, it is treated with colchicine (See Fig. 45). This is how a new viable hybrid cereal of wheat and rye first arose. It is a new genus called *triticale*, an intergenic hybrid that has the characteristics of both its parents—wheat and rye, See. Fig. 46.

Although the triticale breeding programme began as early as 1945, it was only in 1959 that it became possible to evolve




First-generation triticale seeds are usually sterile even though they may germinate. The sequence at top shows how the sterility is overcome by treating seedlings with the alkaloid colchicine Application of this substance to the tip of a growing sprout interferes with mitotic division of cells in such a manner that the number of chromosomes is doubled. The doubled chromosome complement gives rise to fertile flowers that later grow on the stem. The seeds produced are also usually fertile. Some wheat-rye hybrids produce seeds that will not germinate, and embryo culture is required to produce first-generation seedlings. The technique, which is shown in the sequence at bottom, consists in excising the embryo from seeds that are immature (14 to 20 days fertilization) and culturing the embryo in an agar medium. The culture is kept in the dark until the embryo sprouts and then is kept in constant illumination. Later the sprout is transplanted to a peat pot and treated with colchicine.

Fig 45

Breeding of triticale (T) begins (a) with a cross between wheat (W) and rye (R). The first-generation triticale plant ($F_1$), is made fertile with colchicine treatment, and the resulting seeds become the second generation ($F_2$). This generation and subsequent ones can be backcrossed to either parent or crossed with entirely different varieties of wheat or rye (b, c). Triticale-triticale crosses are also made (d). A primary triticale is one that is obtained from a wheat and rye cross or from crossing two triticales, each obtained from the same wheat and rye species. A secondary triticale is the result of crossing different varieties of triticale or of crossing a triticale with a wheat or a rye that was not a parental stock.

Fig. 46

a genetically viable plant. Even so the crucial step in its evolution came not by design but rather as the result of an accidental out-cross. As Borlaugh, the leader of the programme, observed, to restrain the arrogance of "genetic engineers", "the largest and most important step toward making the break-through in triticale improvement was executed by capricious mother nature herself". On a March morning in 1945 when "one promiscuous, venturesome stray wheat pollen grain with a potent and valuable 'genetic load' from the nearby wheat breeding plot floated across the road under cover of darkness and fertilised a sad but permissive tall, sterile degenerate triticale plant". Thanks to this chance fertilisation there arose a year later (two generations) several unusually promising plants in a segregating population. Their genetic makeup clearly indicated the value of the illicit stray wheat pollen grain. Its triticale progeny was free of several defects. It was dwarf and had completely overcome the sterility barrier which had inhibited progress in triticale improvement for decades.

The sterile triticale plant was a tall hexaploid cross called X308. The wheat pollen that fertilised it was most likely a Mexican dwarf bread wheat. The progeny of X308 and the unknown dwarf wheat are now called Armadillo. By further selection many fully fertile Armadillo strains have been produced, compared and standardised. They have two main advantages over wheat. First, in comparable conditions they seem to give higher yields than wheat. In an experimental farm triticale yielded 8.3 and and 7.2 tons per hectare. Second, its protein content usually surpasses that of wheat even though as in wheat and rye it varies with cultural conditions. With these advantages triticale bids fair to be the first man-made cereal grain to compete successfully with the traditional cereals all of which were selected by our primitive ancestors long long ago. Its production is the first real break with our past agricultural tradition when man is not domesticating a wild species but creating an entirely new one. It seems likely that triticale will become an important food crop during the coming decades.

# CHAPTER XI

# *Population Genetics*

We have so far applied Mendels' laws of heredity to investigate the alikeness or unlikeness between a given couple and their offsprings. In the simple experiment of crossing a tall plant with a short one, we examined the proportions of the kinds of plants arisen from the seeds. This is an exercise in individual genetics. Population genetics, on the other hand, is concerned not with the outcome of any individual mating but with the statistical consequences of Mendelism in *groups* of individuals called populations. It studies the hereditary phenomenon on a populational level.

When we study genetics of a population as apart from that of an individual, a number of differences immediately arise. The most important of these differences stems from the fact that while individuals come and go, populations virtually remain forever. Accordingly it is pertinent to enquire whether the genetic composition of a population remains constant from generation to generation and, if not, how fast or slow is the change. The study of population genetics is therefore inevitably related to that of organic evolution, which from the genetical viewpoint, is but a process of cumulative change in the heredities characteristic of species.

As we remarked in Chapter I, this process of cumulative change in the genetic composition of populations that is evolution could not be accounted for by Darwin's idea of natural selection leading to the "survival of the fittest". Since appearance of an organism must necessarily precede its survival, an adequate theory of evolution had to discover the machanism of heredity to explain how the "fittest" came to arrive in the first instance. Mathematical biologists like J.B.S. Haldane, R.A. Fisher, Sewal Wright, and others have done exactly this. They have applied Mendelian principles to mass matings to build up a mathematical theory of evolution in much the same way as mathematical physcists like Maxwell and Boltzmann built up kinetic theory of gases by considering the random motions of swarms of molecules instead of individual molecules on the basis of Newton's laws of motion. In the same way mathematical biologists have established a number of laws or principles governing the evolution of populations. We shall begin with the simplest of these laws, the Hardy-Weinburg Conservation law which prescribes the necessary and sufficient conditions for a population to conserve its genetic composition. It is the limiting case when there is no evolution with the population remaining so to speak in a genetic straitjacket.

To derive Hardy-Weinburg Conservation law let us first consider an individual mating of a heterozygote tall plant Yy with another heterozygote Yy described in Chapter III. As will be recalled, the probabilities or frequencies of recurrence of three genotypes YY, Yy and yy are respectively $\frac{1}{4}$, 2/4, $\frac{1}{4}$, their sum adding up naturally to unity. It will be seen that while the *gene* probabiiity or frequency of each allele Y and y is 1/2—there being in all four alleles two of each type Y and y—the probabilities or frequencies of the three genotypes YY, Yy, yy to which they lead are respectively $(\frac{1}{2})^2$, $2(\frac{1}{2})$, $(\frac{1}{2})$, $(\frac{1}{2})^2$. This is only a particular case of a very general theorem that holds even when gene frequencies do not happen to be equal as in the aforementioned illustration. Suppose the probability of Y is some number p instead of $\frac{1}{2}$ and that of y some other number q, the sum of p and q being unity. It can be shown that the

frequencies of the genotypes YY, Yy, yy will respectively be

$$p^2, 2pq, q^2.$$

Again the sum of the three frequencies $p^2 + 2pq + q^2 = (p + q)^2$ is unity, as it ought to be. This is the celebrated Hardy-Weinburg theorem referred to above.

To prove the theorem consider a population of N individuals who are assumed, for the sake of simplicity, to have only two alleles Y and y at a particular locus. Such a population will obviously be a mixed assortment of only three genotypes YY, Yy, and yy. Let D individuals be dominants (YY) H hetrozygotes (Yy), and R recessives (yy) so that D+H+R equals N, the total individuals in the population. The gametes of the dominant (YY) will carry only the allele Y and those of the recessives (yy) only the allele y. But those produced by the heterozygotes Yy will produce gametes half of which will carry Y and the other half y. The totality of these 2N gametes constitute what we may call the gene pool of the population in question. Of the 2N gametes in the gene pool (2D+H) will obviously carry Y genes and (2R+H) will carry y genes. Hence the frequency or probability p of the Y gene will be $\frac{2D+H}{2N}$ and the frequency q of the other allele y will be $\frac{2R+H}{2N}$. We can now compute the frequencies of the three genotypes in the next generation by the usual chequerboard method employed in Chapter III. For it is intuitively clear that the total upshot of random mating between individuals of this population, and the subsequent random union of gametes produced by the mates, is equivalent to complete random union of all the gametes in the "pool". Now if the frequency of the allele Y is p and that of allele y, q, where $p+q=1$, the frequency of the genotypic combination YY will be $p^2$, that of Yy will be $pq+qp$ and that of yy $q^2$ as a glance at Fig. 47 will readily show. The frequencies of the three genotypes YY, Yy, yy in the next generation as a result of random mating will therefore be respectively $p^2$, $2pq$, $q^2$.

Now in the new generation again the gene frequency of the allel Y is obviously the sum of the frequency of the dominants (YY) and half that of the heterozygotes (Yy). It is therefore

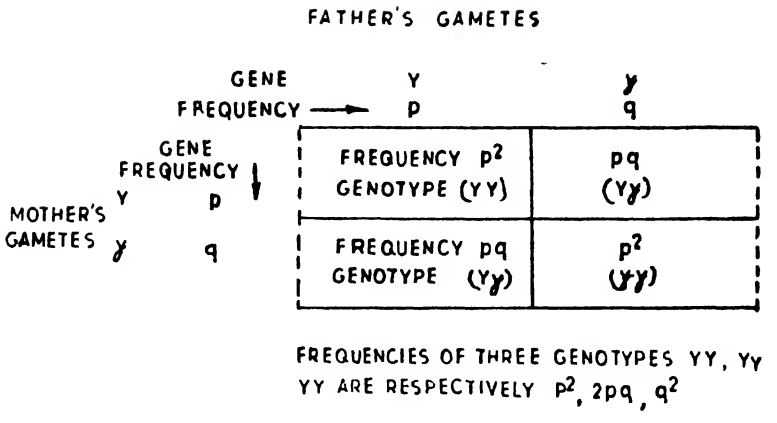



Fig. 47

$p^2+\frac{1}{2}(2pq) = p(p+q) = p$ as $p+q=1$. Similarly, the frequency of recessive allele y is $\frac{1}{2}(2pq) + q^2 = q(p+q) = q$. It therefore follows that the frequencies of the genotypes YY, Yy, yy in the next generation will again be $p^2$, 2pq, $q^2$ respectively. In other words, the population is in a state of equilibrium under random mating. By "equilibrium" we simply mean that there is no change in the genotypic proportions in the population from one generation to another. This implies no changes in the gene frequencies as well. There are, no doubt, many other types of equilibrium conditions; but the instant case of equilibrium under random mating is the simplest. It is known as the Hardy-Weinburg Conservation law because it was discovered independently by the mathematicians G.H. Hardy and W. Weinburg in 1908.

Hardy-Weinburg law is actually stronger in that even if a population is initially not in equilibrium proportions, equilibrium is reached after a single generation of random mating. Thus suppose the initial frequencies (d, h, r) of three genotypes in population are respectively 0.1, 0.3, 0.6 so that gene frequencies are respectively $p=0.1+\frac{1}{2}(0.3)=0.25$ and $q=0.6+\frac{1}{2}(0.3) = .75$. The genotypic frequencies then become $p^2=.0625$, $2pq=.375$ and $q^2=.5625$ in the next generation, which from then on will remain the same in all subsequent generations as long as the system of random mating continues

to hold. In fact, all populations with the *same* gene frequencies, no matter what their initial genotypic proportions may be, will attain the same equilibrium condition on random mating. Thus, both the populations (.1, .3, .6), (.2, .3, .6), (.2., .1., .7) whose gene frequencies p and q are the same, namely, .25 and .75 respectively become (.0625, .375, .5625) in the next generation on random mating

We thus observe that with two variants or alleles Y and y of a gene any given population with initial genotypic frequencies (d, h, r) stabilises itself in an equilibrium state ($p^2$, 2pq, $q^2$) in a single generation under random mating where $p=d+\frac{1}{2}h$ and $q=\frac{1}{2}h+r$. This Hardy-Weinburg Conservation law may also be symbolically expressed as

$$\begin{array}{llll} (Y+y)^2 & = YY & 2Yy & yy \\ p \quad q & p^2 & 2pq & q^2 \end{array} \qquad (1)$$

The advantage of this symbolic representation is that it suggests an immediate extension of the equilibrium law to populations involving multiple alleles. For example, with three alleles Y, y, y whose frequencies are p, q, r respectively with $(p+q+r=1)$, the proportions of the six genotypes in a large random mating population are given by

$$\begin{array}{llllll} (Y & y & y)^2 & YY \quad Yy & Yy \quad yy & yy\ yy \\ p+q+r= & & p^2+2pq+2pr & +q^2+2qr & +r^2 & \end{array} \qquad (2)$$

It can be shown that the genotypic frequencies are in actual equilibrium state. For the gene frequencies are conserved from one generation to another. Thus the output of Y gametes in the succeeding generation is obviously $p^2+\frac{1}{2}(2pq)+\frac{1}{2}(2pr)=p^2+pq+pr=p(p+q+r)=p$. Similarly, the output of y and y gametes is found to be q and r respectively. If an initial population is not in equilibrium state, the condition (2) will be immediately established after one single generation of random mating exactly as in the case of two alleles.

It will thus be observed that no matter whether a gene has two alleles or more, Hardy-Weinburg Conservation law ensures the stability of a population with respect both to gene and genotypic frequencies under conditions of random mating provided no other influences such as migration, selection, mutation, etc. intervene. There is then no inherent tendency

for its genetic properties to change from generation to generation and therefore no evolution. But in a natural environment other influences do appear. In fact, the gene as well as genotype frequencies are continually altered during successive generations under several pressures. Among them the most important are four. First, there is the mutation pressure due to recurrent change of a given sort in the gene. For, although genes are normally transmitted unchanged, they are now and then spontaneously altered or mutated by rare but uncontrollable microchemical accidents. Having occurred, the mutation persists and is transmitted. Second, there is the immigration pressure due to introduction of different heredity by the influx of outsiders from without. Third, there is the selection pressure due to any systematic cause by which the gene tends to increase or decrease in frequency without either mutation or immigration. Differential mortality, differential rate of attainment of maturity, differential mating, differential fecundity and differential emigration are such causes. Fourth, there is the pressure of random fluctuations also called genetic drift due to accidents of sampling. For, in actual practice the gametes, that transmit genes to the next generation, carry only a sample of the genes in the parent population. Consequently, unless the sample is very large, the gene frequencies are liable to change between one generation and the next.

Fisher, Haldane and others worked out mathematically the effects produced by pressures of various kinds such as those listed above. Consider, for example, the effects of selection, that is, the differing 'fitness' of the individuals in the population to breed the next generation. If these differences of 'fitness' are in any way associated with the presence or absence of a particular gene in the individual's genotype, then selection operates on that gene. As a result, its frequency in the offspring is not the same as in the parents, since the parents of different genotypes pass on their genes unequally to the next generation. In this way, selection causes a change of gene frequency and consequently also of genotype frequency.

Haldane devised a neat way of measuring the 'fitness' of the genotypes to breed their kind and thus the intensity of selection pressure. Suppose the selection acts against the gene y.

As a result one of two things may happen. Either the genotype y y may be discriminated against or both the genotypes Y y as well as y y which carry y. If the coefficient of fitness of an unaffected genotype is taken as 1, that of a discriminated genotype may be taken as 1—s where s is some positive proper fraction. Let us assume for the sake of simplicity that only one genotype yy is discriminated against. Then the initial genotype frequencies or probabilities as well as their fitness to breed the next generation will be:

| Genotypes | Y·Y | Yy | yy |
|---|---|---|---|
| Initial frequencies | $p^2$ | 2pq | $q^2$ |
| Coefficient of fitness | 1 | 1 | (1—s) |

As a result the frequencies of the three genotypes in the next generation will be in the proportion $p^2 : 2pq : q^2(1—s)$, where each proportion is the product of the original genotype frequency and its corresponding coefficient of fitness. To convert these proportions into their corresponding frequencies or probabilities all we need do is to multiply each one of these three numbers by the same normalising factor, $\frac{1}{1-sq^2}$ in order to ensure that the sum of three frequencies adds to one. The genotope frequencies in the two generations will therefore be as follows:

| | YY | Yy | yy | Total |
|---|---|---|---|---|
| Initial genotype frequencies | $p^2$ | 2pq | $q^2$ | 1 |
| Genotype frequencies after selection during the next generation | $\frac{p^2}{1-sq^2}$ | $\frac{2pq}{1-sq^2}$ | $\frac{q^2(1—s)}{1-sq^2}$ | 1 |

This is typical of the way in which it is possible to compute frequencies of genotypes in the next generation after allowing for the various kinds of pressures There are, of course, many complications ignored in our illustration. For example, a rather complex situation arises when the gene in question happens to be sex-linked like the hemophilia gene. Alternatively, different genes located in different chromosomes or

even in the same may also be linked in the sense that the hereditary transmission of one includes or excludes the other.

To enable mathematics to take account of some of these manifold complicating factors, Haldane, Fisher, Wright and others devised several neat stratagems by resort to matrix algebra, differential and integral equations, etc., the final aim in each case being the computation of the genotype frequencies in the next generation. For, if we succeed in deriving them, we can always calculate the change in gene frequency from one generation to another and thus measure the effect of selection or other kinds of pressure on gene frequency from one generation to another.

As a result of these mathematical investigations, we are able to derive many interesting results, among them the effect of various influences like those of selection, mutation, competition, etc., on the genetical qualities of populations. Thus it can be shown that the effect of selection is often balanced by that of mutation. For instance, in the case of haemophilia gene, Haldane computed that something less than one-third, perhaps one-fourth, of all such genes are wiped out in each generation because of the tendency of haemophiliacs to die young. Consequently, there must be some source from which they are replaced. For if not, a diminution of 25 per cent per generation would require the entire male population of England to be haemophiliacs at the time of Norman conquest. Since this could not be the case, haemophilia genes must be arising spontaneously by mutation at a rate equal to that at which they are being wiped out to keep the frequency of haemophiliacs at a constant level.

At the time Haldane made his calculations heamophilia was an incurable disease and even a royal prince like the Russian Prince Alexis of the ill-fated Romanov dynasty died young before reproductive age. This is no longer the case. A heamophiliac can nowadays be kept free from fatal heamorahages by appropriate use of very expensive products derived from normal human blood. As a result the proportion of both actual heamophiliac males as well as female carriers of heamophilia is rising. This is true not only of heamophilia but also of all genetic defects that we may be able to cure medicaly or

surgically. Thus the more we succeed in curing genetic diseases that are otherwise fatal, the more we increase the frequency of such lethal or semi-lethal genes in the population. In the long run, therefore, all that medical science has accomplished is to increase the prevalence of the disorder. There seems no way out of the medical dilemma of our time to which we have already alluded in Chapter VIII.

But, to revert to Haldane's calculations, he also showed that, under certain conditions, the number of generations required for a given change in population is inversely proportional to the intensity of selection. As a corollary, he deduced that selection is rapid when populations contain a reasonable proportion of recessives but very slow, in either direction, when recessives are rare. He thus provided an explanation of the fact noted earlier that lethal genes are usually recessive and its converse, that the only new types which have been known to spread through a wild population under constant observation are dominants.

However, mathematical biologists have not remained content merely finding mathematical explanations of known facts like the prevalence of dominant types. They have also computed theoretically the changes in the character of populations exposed to various kinds of pressures which experiments could confirm or deny. Many of these theoretical predictions have actually been verified by observing the alterations induced in a population by its exposure to natural selection under controlled conditions. This was done with populations of flies by Dubinin in the Soviet Union, by Dobzhansky in the United States, Kalmus in England and Teissier in France. Mathematical theory of organic evolution has thus had the imprimatur of experimental confirmation. We can therefore readily accept the theory that the main motive force of organic evolution has largely been natural selection, even though the actual steps, by which individuals come to differ from their parents, are due to causes other than selection. Consequently evolution could follow only certain paths chalked out by other influences like competition, mutation, etc.

While the results of these mathematical explorations in the field of genetics are of great value to the specialists, they have

yielded to the lay citizen even a richer bonus. For it has unequivocally demolished the earlier misunderstanding that natural selection, the motive power of organic evolution, is a sort of Hobbesian war of all species against all in which the "weak" go to the wall and only the "fittest" survive. The natural selection is no longer deemed to be relentless war. It is simply competition tempered with co-operation. For pugnacity and aggressiveness are often less conducive to biological success than is inclination to 'Live and let live' and to co-operate with other individuals of the same species and of others. As T. Dobzhansky has remarked, "Natural selection is neither egotistic nor altruistic. It is, rather, opportunistic; life is promoted now by struggle and now by mutual help."

It is, therefore, no surprise that animal communities exhibit a wide spectrum of behaviour ranging from mutual aid to ruthless competition according to circumstances. A community may even oscillate between tender parental care and cannibalism of its offsprings according to requirements. This is shown by observing the behaviour of animals that lend themselves well to laboratory experiments such as fruit flies (Drosophila), flower beetles (Tribolium), tropical fish, mice and rats. They all show that where a population is established in a closed space, under the best conditions the experimenter can devise, the population does not build up indefinitely but reaches a ceiling level where it remains steady provided sufficient food and other daily needs are supplied and metabolic wastes removed. In some cases, experiments have been repeated again and again and almost the same population ceiling reached each time. The populations reach these stationary optimal levels without the intervention of the usual Malthusian checks-shortage of food supply (famine) pestilence (disease), and predation (war). More than enough food is provided, the physical environment is kept clean in order to exclude disease-causing organisms, and there are no predators.

In such an ideal environment experimental populations can sometimes be kept going for generations with reproduction just keeping pace with senile death so that population remains stationery at its ceiling level. The means by which an automatic balance between births and deaths is achieved vary

from one species to another. Guppies (Lebistes), the well-known aquarium fish, regulate their numbers by simply eating a proportion of their new born young varying the amount of cannibalism as required. In flour-beetles there are several mechanisms working in parallel to limit the population explosion, including the remarkable production of a toxic gas from specially developed glands which reduce fertility and increase death rate among the larvae. In mice, some or all of the adults stop breeding—when the ceiling is reached, or alternatively some of the litters of young that are produced receive inadequate milk or mother care and fail to survive. In all cases if the experimenter removes part of the population and so thins it down, the restraints are automatically relaxed and numbers again increase to the former ceiling.

These experiments reveal the existence of homeostatic mechanisms that act internally and have apparently been evolved to prevent numbers from exceeding a density at which life would eventually become insupportable. Similar homeostatic mechanisms seem to have also arisen in wild populations to limit numbers at a safe level and to do so reliably, automatically and from within. They also existed in human societies in the past when human population began to grow and with the advent of neolithic revolution the surplus numbers congregated in cities and towns. Infection then became the homeostatic mechanism to keep a balance between human births and deaths. Now that advance of medicine has all but exorcised it, it is perhaps our greatest misfortune today that no homeostatic control of reproduction remains any longer in the civilized races of men as it exists in the case of animals like fish and game. It is self-evident that the only way to avert the chaos and catastrophe to which its absence is inexorably leading us is to segregate sex and reproduction. Unfortunately, such segregation is likely to be least effective precisely where it is needed most—the poor developing countries of Asia, Africa and Latin America. For these countries have yet to acquire the affluence without which their people can neither have the motivation nor the means and know-how to enjoy sex without reproduction. And yet unless

they are enabled to do so the doomsday predictions of neo-Malthusian demographers will inevitably come to pass much sooner than many of us would like to admit. It is even likely that the future historians may speak of an age of scientific discovery and technological reconstruction that began with the advent of industrial revolution two centuries ago and perished lemmingwise a century hence in an avalanche of numbers way beyond the capacity of earth's ecosystem to support.

# CHAPTER XII

# *Genetics, Lysenko and Lamarck*

In the early 1930's after Stalin had established himself as virtual dictator of the Soviet Union he launched his great campaign to "socialize" agriculture in order to counter the continued fall in agricultural production during the twenties. He began it by plunging head-long into large-scale collectivization and liquidating the more prosperous peasants who were condemned out of hand as *kulak* saboteurs. The goal of the collectivization campaign was the achievement of maximum agricultural production immediately at minimum financial outlay rather than a genuine concern for an all round development of agricultural production and increase in soil productivity. With this goal in view what Stalin wanted was an agrobiology that could accelerate the production of high yielding varieties of plants and animals to keep pace with his planned "leap-forward" in agriculture and animal husbandry. If the classical agrobiologists and geneticists like N.I. Vavilov were too conscientious to promise the spectacular break-through that he so ardently desired, there were others like T.D. Lysenko who were unscrupulous enough to do so. The conflict with scientific genetics in the Soviet Union thus did not originate with Lysenko. It originated with Stalin who wanted an ersatz to satisfy his aims and ambitions if the real one refused to oblige. Lysenko was thus only a consequence

of this conflict and not its cause. But for Stalin's absolute supremacy and overwhelming desire to "industrialize" Soviet agriculture and animal husbandry with hot-house haste Lysenko would have remained an obscure provinicial breeder and a crank theoretician of a bizarre biology.

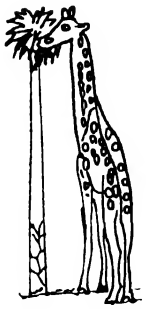
Nevertheless, the rise of a fanatical charlatan like Lysenko to a position of absolute control over both research in biology as well as practical agriculture in a socialist society like the Soviet Union dedicated to the betterment of the-loft of workers and peasants remains an enigma. No single explanation like the emergence of Stalinist 'personality cult' seems to suffice. Part of the answer lies in the extreme complexity of genetics itself.

As late as the thirties genetics was still a *terra incognita*. The great discoveries of molecular genetics—the role of DNA in the mechanism of inheritance, its structure, unfolding of the genetic code, synthesis of a gene—were two to three decades away. The heredity-environment interaction was imperfectly understood. Indeed, in one branch of genetics—bacterial genetics a majority of microbiologists believed in the hereditary transmission of acquired characters, an ancient dogma revived by Lamarck in 1809. Till the spectacular advances in the genetics of bacteria and protozoa during the fifties bacterial genetics remained the last stronghold of Lamarckism as we shall see more fully soon. If the disentanglement of heredity environment interaction proved so difficult in the case of simplest organisms like the unicellular protozoa and bacteria, it is no wonder that the complexity of this interaction in the case of higher plants and animals has not yet been fully understood. It is greatly compounded by the inaccessibility of their reproductive mechanism and long duration of their reproductive cycle. Both have been a perpetual problem to natural scientists concerned with their evolution and heredity. The great Darwin himself, ignorant of Mendel's laws of heredity as well as of gene mutations, was quite puzzled about the origin of variation of species on which natural selection could operate. In his puzzlement he reverted to an earlier speculation of Lamarck, who held that the species of today were derived from those of earlier times by

an adaptation brought about by their desire to fit it more closely with their environment.

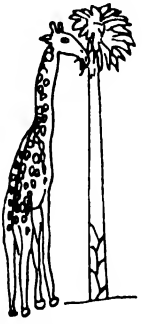
Lamarck recognized several ways in which the environment brings about changes in plants and animals, and it is significant to note that his attention was directed more particularly to the adaptive character of the response which, as Henri Bergson pointed out, implies the teleological, or purposeful, nature of the result. In plants the response is direct and immediate; i.e., not through the mediation of a central nervous reaction system, since this is absent in plants. In animals the adaptive changes are supposed to be more indirect. According to Lamarck, a new environment calls forth new needs *(besoins)* which the animal seems to satisfy by some effort. Thus new needs engender new habits which modify the parts cumulatively and permanently. Conversely, the disuse of other parts leads to their atrophy. It is the resulting material alterations that are inherited. For example, birds that need to rest on water in order to find their food stretch their feet when they wish to swim. The skin becomes accustomed to being stretched and forms the web between the toes. The horns of ruminants have resulted from the ruminants' butting their heads together during combats. But his most celebrated illustration is that of the giraffe. This animal, seeking to browse higher and higher on the leaves of trees on which it feeds, stretches its neck. The stretching continuing as a habit for a long time in all the individuals of the species led to the giraffe's lengthening its front limbs and neck. These naive examples constitute some of the evidence on which Lamarck rested his theory. Although the theory seemed far fetched and was even ridiculed in a celebrated comic strip at the time, Lamarckism, *faute de mieux*, remained in vogue for a long time. (See Fig. 48.) As C.D. Darlington remarked as late as 1955, Lamarckism is the "evergreen superstition".

After the rediscovery of Mendel's laws of heredity, however, Lamarckism was finally rejected as every effort made to transmit acquired characters was seen to have failed. Domestic dogs have had their tails curtailed for many generations but everyone of their descendant puppies is born with its tail intact. For a much longer period Jews and Mohammedans



. DIS DONC, PAPA, POURQUOI QUE LES PALMIERS SONT SI GRANDS ? C'EST POUR QUE LES GIRAFES PUISSENT LES MANGER, MON ENFANT, CAR...

.SI LES PALMIERS ETAIENT TOUT PETITS, LES GIRFES SERAIENT TRES EMBARRASSEES.



..MAIS ALORS, PAPA, POURQUOI QUE LES GIRAFES ONT LE COU SI LONG ? EH BIEN! C'EST POUR POUVOIR MANGER LES PALMIERS, MON ENFANT, CAR ....

... SI LES GIRAFES AVAIENT LE COU COURT, ELLES SERAIENT ENCORE BIEN PLUS EMBARRASSEES.

English translation of captions may be seen on page no.183 (foot notes)

Fig. 48

have had their male babies circumcised and yet their boys are still born unmutilated. Nevertheless, the core idea underlying Lamarckism, that the environment must in some way direct the course of changed inheritance to an obvious advantage of the organism seems to have persisted and is still ardently adhered to by many animal breeders. This may seem odd. But genetic reality is no simple matter. It is so elusive and impalable that any attempt to embody it in words and symbols of our invention makes it one-sided and incomplete.

This is why one may say of it what Herman Hesse said of truth: "in every truth the opposite is equally true".

It is a tragic consequence of our life that since we first discover the world through language we are apt to mistake language for the world. As Jean Paul Sartre has remarked somewhere, our most persistent illusion is that we can catch living things in the trap of phrases, and if we put words together ingeniously enough the reality would become entangled in the signs. Even expression of mathematical reality, the most precise though formal language system we have hitherto devised, has not yet been so entangled. For Kurt Godel has shown that if any logical system that includes arithmetic contained a proof of its consistency and completeness it would also contain one of its inconsistency and incompleteness. It is, therefore, inevitable that the laws of science that scientists have formulated should be riddled with many caveats and contradictions. Quantum physics is a case in point. If a beam of light is a *continuous* wave, its opposite, namely, that it is a *discrete* photon is also true. Likewise, if a nuclear entity like an electron is a *discrete* particle, it is also a *wave* diffused over a continuum. Physicists have now learnt to live with such contradictions by calling it "complementarity". Which is merely to say that neither description gives a full account of the complex way light and matter in their most elemental forms behave. It is, therefore, no surprise that with the advance of knowledge the same duality should manifest itself in genetics as well. As we have seen repeatedly, biological inheritance is transmitted through the action of genes on the ambient environment. But does environment also modify heredity? The answer did not seem to be as unequivocal three decades ago as now. It is true that in the higher animals and plants acquired characteristics are not transmitted. But in the lower organisms such as protozoa and bacteria with life cycles measured in minutes instead of months microbiologists did seem to observe transmission of *acquired* characters. Thus in a number of papers (1913-54) V. Jollos showed that environmentally produced changes in a unicellular organism called *Paramecium* could continue through several cell

generations even in the absence of the causative agent although they would disappear by stages or even in a single generation. These and other observations gave bacterial genetics the dubious distinction of being the last stronghold of Lamarckism. This retention of Lamarckian ideas among the older microbiologists during the thirties and early forties is perhaps natural, if we recall that in studies with bacteria and protozoa we usually deal not with individuals but with huge populations measured in millions of organisms that can and do proliferate at an ultrarapid rate. Such a state of affairs does not permit identification of changes in individual organisms. In practically all older bacterial studies changes in heritable characters which may have occured in single cells remained undetected until such altered cells had given rise to many progeny. As a result, what was observed among many bacteria was change in populations rather than a change in individual cells.

Prior to the development of a recognised discipline of bacterial genetics, such population changes were interpreted primarily in Lamarckian terms as adaptations to environmental influences. There were, of course, variations on this basic theme as, for example, Jollos's interpretation of his experiments referred to above. He called them Dauermodifikationen (lasting modifications) which are environmentally induced adaptive changes persisting, without affecting any inherent factors, for many generations after the removal of the inductive environment. Only a small minority of early investigators recognised bacterial variation as a phenomenon that can involve the occurrence of spontaneous and undirected changes (mutation) in one or few cells which are subsequently selected under appropriate environmental conditions. But the last-mentioned (correct) interpretation, bringing the basic mechanism of changes among bacteria in line with those known in higher organisms, could gain universal acceptance only after the discovery of the structure of the hereditary material (DNA) during the fifties. It was then realised that Lamarckism, as it is understood in the higher forms of life, cannot apply to the lower unicellular organisms, where there is no separation of soma (body) and germ plasm. Induced

changes in the germ plasm are known to be heritable, so that in bacteria and protozoa we would expect a number of the modifications that they acquire to be inherited. It was thus inevitable that this kind of inheritance would be cited as evidence of the inheritance of acquired characters before the discovery of the importance of DNA in the machinery of heredity.

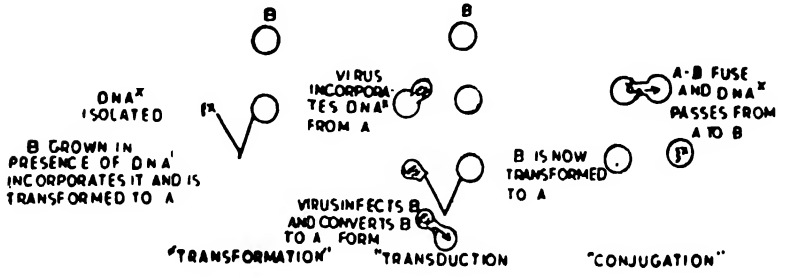
The first glimmer of the new understanding that the basic mechanism of changes in protozoa and bacteria is the same as in higher plants and animals, namely, mutation, came with O.T. Avery's celebrated experiment with the bacteria that cause lobar pneumonia, the pneumococcus, in 1946. He produced a change from one type of pneumococcus to another by the addition of a nucleic acid of the second type. His work was the first overt demonstration of the existence of genetic material (DNA) that could carry genetic information between cells as well as from one generation to another at a time when the nature of DNA itself was only dimly perceived. Subsequent experiments have confirmed that it is the availability of the appropriate DNA, the carrier of heredity, in the nutrient in which bacteria grow that is responsible for induced and transmissible alterations in bacteria. A.D. Hershey and R. Rotman went a step further. They showed in 1949 that even virus particles that attack bacteria (bacteriophages) can exchange, segregate and recombine their hereditary factors and can act as carriers of hereditary material (genes) from one strain of bacteria to another.

Since then much work has been done on this "transformation" phenomenon. Its essential feature may be summarized by saying that transformation occurs in only small proportion of the bacteria exposed to the transforming DNA and that in each case it represents the incorporation of only a small unit of DNA donated by the donor bacterium (A) into *the right place* in the DNA repository of the recipient (B). (See Fig. 49.) There it places the original segment and establishes itself as part of the bacterial cell's inheritable mechanism. Three distinct ways in which DNA carrying a particular genetic character may be transferred from one bacterial strain to

another thereby conferring type A qualities to type B have been discovered :

In the first called *transformation*, chemically extracted ("naked") DNA, or naturally released extracellular DNA, can transfer information affecting one trait, or occasionally two traits, from one bacterium to another related bacterium.

In the second process called *transduction*, informative DNA (again only bits that affect one, and sometimes two traits) is




Three ways in which DNA carrying a particular genetic character can be transferred from one bacterial strain to another so conferring type A qualities on type B.

Fig. 49

transferred from one bacterium to a related one with the aid of bacteriophage. In this process the protein coat of the phage, which assists in the injection of the phage's internal DNA into a susceptible bacterial host cell, packages and transfers bacterial DNA instead of (or in addition to) phage DNA. The bacterial DNA inside the phage originates from the phage's prior bacterial victim, and may become incorporated in the information of the bacteria into which the phage has injected the informative bacterial DNA.

In the third process of *conjugation*, the donor bacterium can contribute a very substantial part, or even all, of its information (in the form of a just replicated set) to the related recipient; the process of transfer of such information requires direct contact between the cells and involves the migration from one cell to the other of a chromosome-like

DNA entity, on which information is arranged in a linear fashion. If the information in the donor's DNA differs from that available in the recipient's DNA, the new information does not become available *in toto* to the progeny following transfer of the informative material. What occurs is an exchange or recombination of the new and the old information of the recipient. The discovery of these three aforementioned processes of transfer of genetic materials in bacteria showed that DNA is the key to heredity of *all* organisms from simple bacterium to complex man.

However, even as experimental observations were converging from all directions to drive out Lamarckism from its last stronghold in bacterial genetics, C.H. Waddington reported a type of adaptive inheritance sponsored by environmental stimuli *not* in the case of bacteria but in a certain strain of flies. He discovered that if such a strain is exposed to higher temperatures during pupal stage, they develop wings with one bar missing—no doubt a trivial variation. But the significant point is that if the process is continued for several generations, flies are produced which breed barless even when the pupal have *not* been heated. The effect is not permanent as after more generations without heating these revert to the normal form. Whatever the explanation, and Waddington offers a complicated Mendelian one, it can be cited as an instance of the inheritance of acquired characteristics.

Although the instance is too trivial and solitary to sustain Lamarckism, as it is usually understood, more striking cases are known where habits and not structures are inherited. The wild canary was chosen some three hundred years ago as a cage bird on account of its plumage alone. It chirped but did not sing. However, bird fanciers in different places managed to teach them different songs, and now each breed of canary, even when brought up from the egg without teaching, sings in its characteristic style. Something similar seems to have occurred in our own inheritance. It is not very long since *homo sapiens* became *homos logos*, a talker. It may have been as short as 200 generations or as long as one thousand according to different estimates. Man must have acquired this capacity

to talk by profound modification of the human brain and ear whereby a considerable area of cerebral cortex has been set aside solely for this purpose, and that without much evidence of selection against dumb type. We are still too ignorant of the mechanism by which such rapid evolutionary changes can be carried out to formulate a theory for the hereditary transmission of acquired *habits* as distinct from physiological structures and traits.

But if our habits and behaviourial repertoire are the result of neuronal wiring in our cerebral cortex, we cannot deny environment a role in the outcome. For we now know that although an infant's brain at birth contains the same number ($10^{10}$) of neurons or nerve cells as the adult, it lacks the elaborate pattern of interconnections between them that characterises the mature brain. To what extent the functional connections between nerve cells are established following a stereotyped genetic blue print, and how much of the organisation depends on neonatal environment are open questions. Recent experiments with animals such as those concerned with the effect of early environmental influences on the development of vision in cats seem to suggest that higher the animal in the evolutionary scale the greater the role environment plays in final development of its brain. Animals lower down the evolutionary ladder arrive in the world with their behaviourial pattern genetically fixed once for all. They, therefore, step into a stereotyped life with no requirement for learning about the world around them. Cases in point are bees who know what to do with flowers, and birds that can navigate over vast distances, all by following genetically inbuilt rules. The higher up the evolutionary scale an animal finds itself the more it appears to have to learn about its environment, and the more it *can* learn. At the top we have man who spends many months after birth as a mewing, puking, helpless infant with scores of tasks to learn; walking, manual skills, language, thinking, etc. With a brain as complex as that of man it would perhaps stretch credibility too far to believe that genes alone are able to carry all the information for weaving the final pattern of interconnections of a manifold of $10^{10}$ neurons that is our brain. The

environment therefore plays its part in shaping the finished product.

Since the old debate about the relative contribution of genes and environment (or nature and nurture as the ancients were wont to say) is still open at any rate in so far as the development of animal and human brain in response to neonatal environment is concerned, it is no wonder that the case for Lamarckism was much stronger forty years ago than today. Indeed, it could then be argued plausibly that environmentally induced adaptive changes are inherited in the case of simpler organisms like bacteria and protozoa. And as life's basic unit, the cell, is alike in all organisms, one could extrapolate the argument by saying that if it can happen in *Paramecium*, it will happen in wheat and cattle too. This is precisely what Lysenko and his followers did in the Soviet Union. They began with the modest claim that the exclusive preoccupation of Western geneticists with the complex molecular mechanisms of reproduction and heredity is an abstract and academic exercise remote from everyday applications. And this was true. They considered it absurd to wait for the unravelling of these mechanisms and give up attempts to alter heredity of plants and animals by more empirical down-to-earth approaches to its control by environmental factors. They began to foster the belief that the quickest way of improving the crops and livestock of their country was not to resort to the traditional time-consuming breeding methods based on Mendelian theory of heredity described in Chapter IX. Now, there are numerous phenomena of inheritance either by direct modification of environment as in flax or through grafting which seem to bear out some of the claims of Lysenko even though no full explanation of their mechanism has been found. By skilfully exploiting some of his earlier successes in plant breeding as well as continually stressing that Marx and Engels following Darwin were staunch Lamarckians, who held that this type of inheritance would guarantee the improvement of the human race, Lysenko managed in course of time to discredit Mendelian genetics as bourgeois, capitalistic and reactionary pseudo-science. But it took him and his collaborators over ten years to do so.

Lysenko made his debut on the national scene with his 1926-27 experiments at the Gandzha (now Kirovabad) Experimental Station on winter planting peas to precede the cotton crop. Whether original or borrowed, from the practical standpoint, they were undoubtedly useful. But he rose to real prominence in 1929 when he first proposed his vernalization technique to reduce losses of winter wheat. In U.S S.R. wheat is sown in autumn. The seeds germinate, but the seedlings do not begin to grow till spring. If the wheat is not sown till spring, it gets a late start, and does not give a good crop. Since in many parts of the Soviet Union the frosts kill seedlings sown in autumn, special breeds of spring wheat had to be used. Even so the yields remained subnormal. Lysenko suggested giving the wheat grains winter treatment indoors. The wheat is stored dry in a granary. In January or February it i wetted and doors opened to give it a few degrees of frost. It is then sown in March or April already germinated, and gets a flying start, so to speak, so that it gives a good harvest. By resort to this vernalization technique it became possible to grow wheat hundreds of miles further north than was possible before. Lysenko was credited with its discovery although it was an ancient practice and had been used elsewhere since the nineteenth century. But what was new was his claim that the practice need not be repeated year after year ! Although this was a revival of Lamarckism, Lysenko's vernalization and other similar proposals won him in 1935 the public support of Stalin. He got it by promising greater, more rapid and less costly increase in crop yields than other biologists believed possible. It is true that at the time the Mendelian school of geneticists led by Vavilov was still a power Lysenko had to reckon with But *ceteris paribus*, Marxist ideology always leans towards those who believe in changing nature rather than contemplating or investigating it. That is why investigators like Vavilov finally lost to "changers" like Lysenko.

As Lysenko's influence increased, he undertook to modify and redefine all biological theory. Some of his innovations were mere exercises in verbalism such as his doctrine of the phasic development of plants. According to this concept the

plant develops in recessive phases, each of which has requirements that differ from those of the other phases; and each plant requirement manifests itself in its own way. Altering one stage in development by environmental means would cause successive stages to be changed. Such changes, he claimed, would be inherited Since his theory of phasic development was incompatible with chromoso nal theory, he redefined heredity as "the end result of environmental changes that have been assimilated during the course of the preceding generations". This led him to deny the existence of genes and dismiss orthodox genetics as an aberration of capitalist science.

Lysenko also claimed that he could produce new types of development cycles in plants by regulating the quality of their nutrients. To do so he first had to shatter the ' conservatism" of the plant and thus render it more sensitive to environmental changes. He shattered this conservatism by using adverse environmental conditions hybridization and grafting. He was specially impressed with the consequences of grafting and held that the stock and the scion (or cutting) so influenced each other that they fused to form a true hybrid. It was thus inevitable that as his power grew he used it to extirpate Mendelian genetics in order to plant his own brand of genetics he called Menchurinism. By 1948 when he was at the acme of his power he decreed the abolition of Mendelian genetics with the consequence that it could not even be taught in the Soviet Union from 1948 onwards. It began to be retaught only in 1945 when he was stripped of his political authority after his protector Khrushchev's fall in the same year. Soviet agriculture and animal husbandry have still not recovered the damage caused by Lysenko's great perversion of genetics by his theory he labelled Minchurinism.

Please tell me paper why are the palms so tall ?
It is to allow the giraffes to eat their leaves my boy.

But then papa, why do the giraffes have a neck so long ?
Well ! it is to enable them to eat the leaves of palm trees, my son, be cause...

...if the palm trees had been too short, the giraffes would have been in great difficulty to eat their leaves.

...if the giraffes had a short neck, they would have been in even greater difficulty to eat their leaves.

# CHAPTER XIII

# *Genetic Manipulation of Life*

As we have seen in the previous chapter, simple unicellular organisms like bacteria and bacteriaphages can exchange, segregate and recombine their DNA, the carrier of hereditary factors, from one strain to another. Before the invention of these novel experimental techniques of changing one strain of a bacterium or virus to another, strain changes occurred *in vivo* by random mutations. The advent of new techniques made it possible to bring about mutations *in vitro* by deliberate design instead of blind chance. This possibility has now encouraged the hope that it will enable us to manipulate biological evolution to produce not only better breeds of cattle and plants but even of men as well. For whereas biological evolution has hitherto relied on random mutations to produce the human species, the human species has now come of age to direct its own biological destiny by contrived manipulation of our genetic patrimony. This is what is sometimes called playing God, or genetic engineering.

The possibility of playing God was first mooted when it was found that "engineered" gene replacements are feasible in simple organisms like *E. Coli*. If, for example, two strains of *E.Coli*—one unable to grow without added tryptophan and

the other unable to ferment lactose—are crossed, a small percentage of the progeny will be "recombinant" type, that is, able to grow without tryptophan and to ferment lactose. At the molecular level, this recombination between the two strains results because of breakage of the parental DNA molecules and subsequent rejoining to form the recombinants. The new techniques of genetic engineering has made it possible to carry out this process of breakage and rejoining of DNA molecules in the test tube. For many years geneticists have used the recombination process to study the nature of genes, but they were confined to studying recombinants of the same or closely related species. The *in vitro* process now enables us, for the first time, to join DNA molecules of unrelated organisms.

The present capability to join DNA molecules *in vitro* is the outcome of past 30 years' research on the properties of DNA and the enzymes or biochemical catalysts involved in cleaving and replicating it. These enzymes are virtually molecular scissors which enable the researchers to cut DNA at sequence specific sites. That is, they enable the segregation of a gene from a DNA molecule and transfer the spliced gene to another DNA molecule. See Fig. 50. We may conveniently

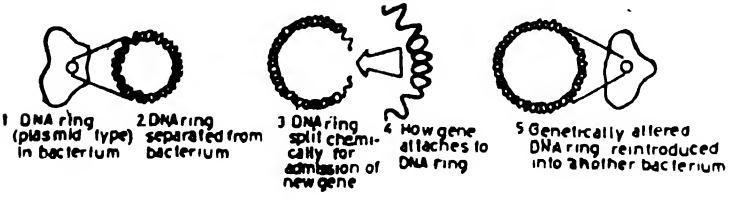



Fig. 50

refer to the former spliced DNA molecule in a recombinant as the passenger and the latter as the vehicle. Two general classes of vehicles have been employed in *E. Coli* host system. It is now possible to employ other vehicle-host systems including mammalian cells in tissue culture. When the recombination *in vitro* between vehicle and passenger DNA is completed, the recombinant DNA must be introduced into the host cell where it can replicate. This is done by a process

known as transformation. It is called transformation because the uptake of a single vehicle-passenger DNA molecule by the cell transforms it into a new strain which then multiplies to form a colony. Any such colony can be propagated indefinitely, enabling one to store or produce (or both) the passenger DNA molecule at will.

Such recombinant genetic manipulations have hitherto been confined to only lower organisms like unicellular bacteria. The reason is the fundamental difference between the cells of bacteria and those of higher plants and animals. The latter have distinct nuclei whereas the former have none. Consequently, exchange of genetic materials between the cells of bacteria is no indication that similar transfer is possible in the case of higher organisms like plants and animals. Even in bacteria, whose reproductive cycle is measured in minutes instead of months, usually only a single factor or gene is transferred at a time. Double characters (e.g. capacity to ferment the sugar mannitol and resistance to an antibiotic like streptomycin) sponsored by two distinct genes may occasionally be transferred simultaneously if the two genes in question are close enough together. But ploygenic characters sponsored by several genes have not yet been transferred.

There are two views about polygenic manipulations of bacteria and viruses. One view voiced by the Noble Prize winner, Sir Macfarlane Burnet, is that they might produce a virulent kind which would be new to world's populations. Nothing could be more disasterous than a "Virgin Soil" epidemic of a new bacterial disease involving the world or even a single city. A case in point is the outbreak of a particularly vicious type of influenza in Europe towards the end of World War I. It was caused by the sudden eruption of a new virus to which the European population had not been immunized. This "Virgin Soil" influenza actually killed more people in shorter time than the War itself during its four-year long duration. He, therefore, advocated a complete ban on such manipulations.

The other view is that although the possibility of a new type of virulent bacterium or virus arising naturally is remote, the likelihood of their emergence by accident in a laboratory

engaged in genetic manipulations of bacteria is by no means negligible. They, therefore, suggest that we should exercise abundant caution very like lawyers do in law suits. They would prefer not to take the risk, however small, especially since so many of their colleagues have shown themselves downright sloppy and careless in their laboratory procedures. Moreover, the dangers of these techniques are not confined solely to the possibility of individual physiological harm. As a silent weapon in biological warfare, newly created pathogenic bugs may be cheaper to use and easier to exploit. No one knows. Indeed, the whole issue of genetic engineering in plants and animals raises other questions that science alone cannot resolve. The undoubted scientific benefits that the techniques will bring will have to be measured against the moral and ethical problems that follow in their wake. For these and other reasons a number of scientists themselves called for certain restrictions on certain types of genetic experiments. Their warning was delivered in the famous letter of Paul Berg and his colleagues in 1945 calling for a ban on genetic research or at least a tight control by stringent guidelines.

During the decade since the publication of Berg letter, the scare of the biohazards of genetic engineering it caused has been found to be greatly exaggerated. As a result genetic engineering research is now being freed from some of the more inhibiting restraints imposed by the guidelines. It is being increasingly realized that the restraints on genetic engineering imposed by Nature are onerous enough. For the modification of the biological inheritance of any organism, even of the lowly bacteria, in any significant manner by other than trial and error is no simple matter. In the case of higher organisms like plants and animals we need to discover what Henderson has compendiously called the "wisdom of the body". For every body alive even the simplest bacterium, is a repository of the accumulated wisdom of 3000 million years of biological evolution on earth. It is likely that its subtleties will always remain beyond our ken. The aforementioned simple, *E. Coli*, for example, has (among other things) to produce some hundreds of enzymes or biological catalysts in appropriate concentration

and spatial location in order to stay alive. A mere description of how it carries out this fantastic feat of chemistry would occupy several volumes even if we came to understand it. For any single enzyme could be the theme for a near life time of good scientific work. But even a complete study of all the enzymes it makes would not bring a molecular understanding of *E.Coli* much nearer. The more we probe the molecular basis of life the deeper grows its myster'. We seem to face here what Sir Macfarlane Burnet has aptly called "an asymptotic brick wall". Which is merely to say that the effort tends to infinity as our understanding approaches completion even in the case of such simple organisms as *E. Coli.*

But higher plants and animals are not simple unicellular organisms like *E. Coli.* They must be studied at three levels: (a) the molecular level (b) the cellular level, and (c) the level of the organism as a whole. There are further complications due to diverse interrelationships between these levels. Because of these complications the application of DNA recombinant technique to higher plants and animals is still riddled with very onerous difficulties. Consider, for instance, the genetic modification of a bacterium like *E. Coli* by inserting therein a synthetic gene. It is not yet clear if the same technique can be applied to higher organisms. The genetic makeup of the latter may prove quite accessible to alteration—for example, by splicing a gene on to a virus and using the virus to infect a sperm or egg. But equally it may not. For animal cells may for evolutionary reasons be specially organized to resist this form of viral usurpation. The present gene-splicing techniques in that case may well prove, in so far as higher organisms are concerned, totally infructuous. But given enough time, the knowledge to manipulate the stuff of life—the ultimate technology—may not prove that elusive after all. It seems likely that genetic engineering will advance slowly by demonstration of its value in the skilful improvement of crop plants and domestic animals.

Next will come a development that may be opposed by some who, like George Wald, advocate that the human genome be declared inviolable. As the develoment in question will be the gene-splice treatment of some of the 1500 human

diseases now known to be of genetic origin, it will almost certainly manage to secure at least a toehold, if not, a foothold on humanitarian grounds. Once genetic engineering technique in human genes, is able to circumvent the genetic manifestation of deleterioue human genes, means of genetic manipulation may then be discovered that enhance the natural process of development and enable each individual to realize his full potential or for that matter create a new human species superior to *homo sapiens*. But all this is a distant dream, because, as already mentioned the possibility of genetic manipulation of forms of life higher than bacteria has not yet been demonstrated.

During the next two decades genetic engineering will, therefore, be confined to the domestication of more and more bacteria for the benefit of man. Already it is possible to "command" the bacterium *E. Coli* to produce the hormone, somatostatin. In this way bacteria will be increasingly turned into "factories" for the production of more complex and useful biological proteins ranging from insulin and other hormones to the enzymes used in industrial fermentation. The insulin breakthrough would be a boon to millions of diabetics, not merely because it would be a lot cheaper but also because this insulin would be an exact duplicate of human insulin thus eliminating the risk of allergy or anti-body rejection of the currently used pig and beef insulin. An equally glittering prize of genetic engineering is the likely manufacture of *pure* human blood protein known as factor VIII, which, as already mentioned in Chapter VIII, is lacking in haemophiliacs and is therefore essential for their treatment. It has now been established that the gene that produces it is located on the X-chromosome. Further the gene has been isolated or cloned and a cDNA clone of factor VIII produced. The first essential step towards a new way of obtaining a *pure* product not contaminated with hepatitis and AIDS viruses has thus been taken. Genetech, the San Francisco based biotechnology company, now hopes to launch its industrial production within two to three years.

Other anticipated rewards of genetic engineering include safer, more potent vaccines, microbial strains capable of

producing larger quantities of antibiotics and other drugs to cure a number of serious diseases. A particularly promising case in point is the use of recombinant DNA technique to overcome the difficulties encountered in the use of interferon as a cure of a wide diversity of viral diseases and cancers. The recombinant DNA technique has led to the isolation of genes that produce human interferon and their cloning or incorporation in bacteria like *E. Coli.* As a result it is now possible to produce in quantity recombinant human interferon by fermentation as well as to purify it by means of nonclonal antibiotics.

In fact, interferon is now being routinely manufactured by bacteria in a battery of 400 litre fermentation tanks at Hoffmann-La Roche, Inc. in the U.S.A. Recombinant DNA carrying a gene for human alpha interferon is inserted in the cells of bacteria *E. Coli.* These bacteria proliferate synthesizing the human protein alpha interferon along with thousands of their own. When bacterial cells reach maximum concentration they are killed, discharged from the fermentation tanks for concentration by centrifugation. The human alpha interferon is then extracted and purified for clinical trials. The extensive trials of interferon efficiency against viral diseases and cancers now under way seem to suggest that it may be possible to tailor interferon molecules to cure particular side effects like fever, chills, minor gastrointestinal upsets, muscle aches, fatigue and anorexia that followed in the wake of earlier use of rather crude interferon. For we are no longer limited to the set of natural interferons. We can now break up interferon genes and splice the pieces to make new genes to tailor interferon molecules to particular effects.

Still other uses of genetic engineering techniques are improvement in the quality of plants. One way of doing so is to combine the qualities of existing crops that are by nature incapable of sexual fusion like imbuing the potato, for example, with some of the qualities of disease resistance found in some varieties of tomatoes. Another is to superimpose on the cereals the capacity possessed by beans, to "fix" gaseous nitrogen directly from the air and thus make their

own fertilizer. This may well prove to be the next big leap after the domestication of wild cereals with which agriculture began. For such a fusion feat can only be accomplished by crossing the sexual barriers that inhibit the production of new varieties by spectacular "marriages" of unrelated plants like wheat and beans. If and when we can devise techniques to overcome these sexual barriers, they may conceivably even enable us to combine the genes of plants and bacteria or of plants and animals leading to a faster production of new and better varieties. If these techniques of fusing the genes of plants with those of bacteria and animals are devised, we may dream of cereals that can thrive in sea water, of potatoes and grains in brackish water, of tomatoes that defy frost, and of other wonders we cannot even imagine now.

We do not yet know when such wonders will come to pass. Researchers are, therefore, presently aiming at more limited goals that may be achieved in the short run. A fairly promising research now under way contemplates the production of nitrogen fixing plants which could dispense with energy-guzzling synthethic fertilizers even though there do not exist at the moment any plants that can do so. The possibility of producing them seems quite real as there exist a large number of plants which have bacteria associated with their roots and the combination can fix nitrogen. One of the nicest things one could do is to make plants that could fix nitrogen without having to have these bacteria associated with them. This again is a long-term project and we do not yet know when it will materialise. But some significant progress has been made in the past decade or so.

Starting with almost no knowledge of the game in 1920 researchers were able to transfer functioning nitrogen-fixing genes from the microbe Klebsiella pneumonia into *E. Coli* in 1922. By the end of the 1920s a detailed map of the cluster of the genes involved with nitrogen fixation in K. pneumonia had been developed. Since the nitrogenenase genes enzyme complex contains only three different protein subunits, this large number of genes was surprising and revealed the great complexity of nitrogen fixation.

Nevertheless, the very fact of transfer of such genes from one kind of bacteria to another has opened the next step of putting these genes into plants. We may, therefore, confidently look forward to many more beneficial applications of DNA recombinant techniques in industry, medicine and agriculture. We now have at hand an extraordinarily powerful set of methods which will allow the further exploitation of living organisms for the benefit of mankind and provide new and improved medicines, food and industrial chemicals. To reap the enormous potential benefits of this new technology microorganisms that are as safe as *E. Coli* but are more suitable for large-scale industrial fermentation will be identified and domesticated. By the end of the century a large variety of passenger vehicle or host vector systems will be developed for industrial use.

## CHAPTER XIV

# *The Selfish Gene*

As will be recalled we remarked in Chapter II that heredity is to environment what programme is to computer hardware. But the mere production of a machine that simulates in some way the behaviour of genes in their biological milieu is no warrant for assuming that both the genes and the machine work in the same way any more than for treating birds and airplanes as identical mechanisms merely because both manage to "fly". Despite the obvious semantic traps lurking beneath the arguments based on such premises some biologists have pushed this rough and remote analogy between them so far as to assign a patently implausible role to our genes in making us behave in the way we do. While all biologists agree that behaviour, like morphology and physiology, is subject to genes preserved by the forces of natural selection, the new school of socio-biologists excessively exaggerates this evident truth to claim that *all* describable behaviour must be the direct product of natural selection. They even explain philandering among the upper middle class as the outcome of their "sex-linked',—or, is it "sex limited"?—genes. This view in its most extreme form was popularised by Richard Dawkins in his controversial book, *The Selfish Gene* he published in 1926.

In the preface to his book Dawkins stated the claim: "We are survival machines—robot vehicles blindly programmed to preserve the selfish molecules known as genes. This is a truth which still fills us with astonishment". It is, indeed, astonishing to learn that the genes we inherit from our parents are not the means to make us what we actually become but rather we ourselves are mere tools to ensure the survival of our genes. In the selfish struggle to ensure their own perpetuation they enslave us and make us behave in the way we do. This theme of our passive manipulation by our gene captors is the keynote of his book. According to Dawkins, "they (the genes) swarm in huge colonies, safe inside gigantic lumbering robots, sealed off from the outside world, communicating with it by tortuous indirect routes, manipulating it by remote control. They are in you and me; they created us, body and mind; and their preservation is the ultimate rationale of our existence. They have come a long way, these replicators. Now they go by the name of genes, and we are their survival machines". He reiterates his thesis in later passages time and again as in:

> "It (that is, the gene) leaps from body to body down the generations, manipulating body after body in its own way and for its own ends, abandoning a succession of mortal bodies before they sink into senility and death."

This means-for-ends inversion of the socio-biologists is about as grotesque as that of Professor Pangloss's demonstration in Voltaire's inimitable satire *Candide* that the nose was formed to bear spectacles, legs were visibly designed for stockings, stones to construct castles and some other similar absurdities. What then is the reason for their view of the inverted relationship between the genes and the organisms to which they give rise?

One reason is the observed fall in fertility of some animals such as rats under the stress of overcrowding. To answer the question why natural selection favours females who reduce their birth rate when the population is overcrowded,

Dawkins invents his "selfish gene" theory. He argues that his theory is better than the usual one that such low-fertility females are prefered by natural selection. But the population selection argument is merely an Aunt Sally set up for the fun of knocking it down. Both arguments Dawkins contrasts take for granted that reduction of fertility is a genetic adaptation for survival under overcrowding. He ignores the possibility that lower fertility may well be an automatic response to altered endocrine function that results from excitment under overcrowding.

It is true that Dawkins in a recent book—*The Extended Phenotype* (1921)—admits that in calling ourselves as "survival machines" in the passage quoted above he "would have been more careful" had he remembered the currently prevailing myths about genes and computers. The myth about genes he has in mind is the general belief that "genetic" effects are irreversible while "environmental" effects are not. This common belief stems from the indubitable fact that while such genetic effects as sex, eye colour, skin pigment, blood group and the like are generally irreversible, environmental effects such as hair coiffure and cosmetic make-up are easily modifiable. The same is true of genetic and environmental diseases. For we do find it much harder to cure (or prevent) genetic diseases like haemophilia, Cooley's anaemia, Hutington's chorea, phenylketonuria, and Dawn's syndrome, to name only a few, than environmental ones such as measles and malaria. Dawkins could not be unaware of what everyone knows, namely, that decrees of heredity are not as easily annulled as those of environment. And yet he dismisses this basic difference between heredity and environment as "pernicious rubbish on an almost astrological scale" and goes on to conclude: "Genetic causes and environmental causes are in principle no different from each other. Some influences of both types may be hard to reverse, others may be easy. Some may be usually hard to reverse but easy if the right agent is applied. The important point is that there is no general reason for expecting genetic influence to be any more irreversible than environmental ones".

It is true that on some rare occasions a genetic effect may reverse itself as when a person changes his (or her) sex. But such reversal is more apparent than real as the change itself is due to some genetic abnormality. It is, therefore, of genetic origin. Likewise, it may be possible in a few cases to mitigate, by recourse to a chemical agent, the ill effects of what Sir Archibald Garrod called "the inborn errors of metabolism" that give rise to genetic diseases. A case in point is the coagulant chemical expressly tailored to coagulate the blood of a bleeding haemophilic. But it can not make his blood normal. Surely such stray exceptions to the norm provide no basis for the broad generalisation Dawkins makes when he puts on a par the irreversibility of both genetic and environmental effects. This paralogical leap is his warrant for calling the common (and correct) belief in the greater inexorbility of heredity vis-a-vis environment a myth.

This is not all. Dawkins proceeds next to deal with another current belief, in the inflexible adherence of computers to instructions programmed into them in the same chevalier way. By a similar sleigh of hand he tries to argue that it too is a myth, the so-called computer myth. This computer myth, he thinks, is almost as deep-scated in the modern mind as its other counterpart, the gene myth. Furthermore, he now concedes that since popular myth associates a robot with rigid inflexibility, his use of the word "robot" in the passage quoted above was admittedly misleading. But such rigid inflexibility was *not* the association he had in mind when he wrote it.

In short, Dawkins admits now that "it was the result of combining these two powerful myths, the gene myth and computer myth, inadvertently" in his previous book, *The Selfish Gene*, that produced the "comic misunderstanding" of its message. It is a devious way of wriggling out of an untenable position he had taken earlier. He might have been more straightforward and admitted that he was so dazzled by the illumination of Darwin's powerful theory of evolution by natural selection that he could not see the bounds of its validity and, therefore, pushed it far beyond the domain of its legitimately admissible explanation.

## CHAPTER XV

# *Heredity and Politics*

Politics of heredity is as old as the ancient city states that emerged in the wake of neolithic revolution and gave politics its first foothold in human societies. Since those days of remote antiquity till almost today the belief has persisted that "blood" is the carrier of heredity so that children are simply the outcome of the "blended blood" of their parents. It is, therefore, no wonder that rulers of the nascent city states convinced of the superiority of their own "blood" should seek to preserve it by recourse to limited inbreeding whereby princes married princesses and not low-born maids or slaves. It is true that there were some royal houses, as for example, that of the Egyptian Pharoahs, which were not content with even such limited inbreeding because of their overweening dynastic self-conceit. They resorted to total inbreeding requiring the heir-apparent to marry his own sister, because no other princess within or without the realm was deemed a fit match for him.

The first to provide philosophic support to these elitist practices of succession by heredity was Plato. His most important dialogue, the *Republic*, was broadly concerned with the construction of an ideal commonwealth. He envisaged such a commonwealth to be a three-tier pyramid consisting of the common people, that is, slaves at the base and the ruling

élite or "guardians" at the summit with the intermediate class of soldiers in between them. The guardians, who alone were to have the monopoly of political power, were to be chosen initially by the legislator. But thereafter their successors were to be their hereditary descendents, even though Plato, in subconscious recognition of what we now-a-days call mutation, admitted exceptional cases, where a promising child of the inferior classes might be promoted and an unsatisfactory one of the guardians degraded. Plato also ordained that the guardians, the group of some men and some women, selected by the legislator, should live communally sharing common houses, meals and even wives To quote the *Republic*, "These women shall be, without exception, the common wives of these men, and no one shall have a wife of his own". A modern version of Plato's proposal is Muller's idea of using the semen of outstanding men for artificial insemination mentioned in Chapter 1. His suggestion of "common wives" must have caused as much stir in his days as that of Muller in our own. Muller died in 1967 and his idea does not seem likely to be brought into practice in any foreseeable future.

But Plato went one better than Muller. He was not content with merely safeguarding the heredity of the guardians. He further developed his concept of population control and, in particular, described his eugenic proposals for public hymeneals of licensed public breeders. These proposals prescribed that at certain festivals, brides and bridegrooms, in such numbers as were required to keep the population constant[1], would be brought together, by lot, as they would be taught to believe; but in fact, the rulers of the city would manipulate the lots on "eugenic" principles. That is, they would arrange that the "best" fathers should have the most children, like the stud bull siring all the cows in a dairyfarm. Moreover, as

[1] In the *Laws*, Plato arrived at the figure of 5040 citizens as the desirable size, adequate to furnish "numbers for war and peace, for all contracts and dealings including taxes and divisions of land" This with dependent slaves would make the total population of the city state about 60,000 people.

in an animal farm all children were to be taken away from their parents at birth, and great care would be taken that no parents should know who were their children, nor vice versa. Deformed children, and children of inferior parents, "would be put away in some mysterious place, as they ought to be". Children arising from unions not sanctioned by the State were to be considered illegitimate. Breeding mothers were to be between twenty and forty and impregnating fathers between twenty five and fifty-five. Outside these ages, intercourse was permissible but abortion or infanticide was compulsory if it led to pregnancy. In the "marriages" arranged by the State, the people concerned were to have no voice, they were to be actuated by the thought of their duty to the State, and not by any of those common emotions that are usually associated with "falling in love".

Although Plato's *Republic*, unlike modern Utopias was perhaps intended to be actually founded, his attempt to do so in collaboration with the younger Dionysius, the tyrant of Syracuse, was a disaster. Nevertheless, Plato's proposal to prevent genetic decay of the ruling élite by selective breeding has, with rare exceptions, been practised by all aristocracies. Belief in the importance of élitist intermarriage remained an old and essential support of aristocratic feudal systems for millennia. It was accepted so axiomatically that it did not require any scientific justification till the rising tide of radical discontent of the later nineteenth century that followed in the wake of abolition of slavery and increasing enfranchisement of the masses. After Tom Paine, Karl Marx, and others had fought for the rights of common man invoking John Ball's old war cry,

> *When ADAM delved and EVE span*
> *Who was then the gentleman?*

it did seem necessary to call in science to buttress the belief that biological inheritance is something akin to passing on property to an heir, like Habsburg chin, with the title to the Holy Roman Empire. Such support did come forth in time from a new biological science ostensibly concerned with

improving the health and welfare of the human species as a whole rather than merely countering the genetic degeneration of only the ruling aristocracy. It was founded by the British biologist, Sir Francis Galton, who called it Eugenics, from the Greek word *eugenia*, meaning well born. He defined Eugenics as "the study of the agencies under social control which may improve or impair the racial (meaning hereditary) qualities of future generations physically and mentally".

Galton, though totally unaware of Mendel's work, was greatly impressed by the power of heredity in man after reading his cousin, Darwin's great work, the *Origin of Species*. He, therefore, set about studying the heredity of men of exceptional ability in Great Britain. He found that many were related and that all belonged to relatively few families. This led him to conclude that those on top were there largely because of their "superior" heredity while those at the bottom owed their lowly status to their "inferior" biological inheritance. He thus attributed a man's worldly success to his heredity alone to the almost total exclusion of his environment. To quote Galton's own words "the foundation and outcome of the human mind is dependent on race", by which he meant heredity.

His main conclusions that upper classes were "upper" because of their genetical superiority to the inferior classes and required protection against the reckless overbreeding of the lower classes were naturally welcomed by the ruling elite especially as they "scientifically" justified their own monopoly of wealth and power at a time when it was beginning to be threatened by the equalitarian socialist agitation of the time. But Galton's argument though spelt out with the highest intentions was specious. He overlooked the historical fact that the British ruling class in his time was a very small minority and very much intermarried, as well as the social fact that the chances of success, even intellectual success, were, as they still are, overwhelmingly weighted in favour of children from upper class families. By unduly exaggerating the role of what he called "nature over nurture" in the upbringing of man, Galton initiated a biological interpretation of mankind with its emphasis on race and breeding. It

affected to a greater and lesser degree even the most progressive thinkers in the social and historic sciences. It was widely popularized by historians like J.R. Green and novelists like H.G. Wells. But in baser hands it was grossly abused as the same argument was used to prove that the Nordics were superior to other white races, particularly to the Jews, and the white races were superior to the coloured. Its full horror occured during Hitler's ascendancy in Germany when the excuse of race superiority, fanatically believed in by thousands of the Nazis, was used to perpetrate under conditions of incredible cruelty and degradation the largest and most senseless massacres in history. It was also the excuse for Himmler most bizarre breeding programme called Lebensborn (Fountain of Life) where Aryan looking women with blond hair, blue eyes, and striking features were mated with SS Bully boys to turn the German population into a race of herrenvolk. Roger Woddis recently parodied both the emollient as well as virulent perversions of genetics in the limerick:

*Let us be moral and discuss*
*(For they are not the same as us)*
*How best to limit lesser breeds*
*And stop them scattering their seeds.*
*A Mrs Shakespeare on the pill*
*Need not have laboured with a Will;*
*Young Dickens would have been undone,*
*And Faraday' the blacksmith's son.*
*And having thus turned back the clock,*
*We can regenerate the stock,*
*Proceeding to our final goal*
*By race, as well as birth control.*
*Nor should we merely help the poor,*
*But open wide the oven door*
*To other groups with less to lose,*
*Like Gypsies, radicals and Jews.*

Although the grosser abuses of genetics to support proposals for very drastic changes in the structure of society

such as the extermination or expulsion of the "unfit" or compulsory sterilization of those with "impure" or "contaminated" heredity are no longer in vogue, lesser perversions of genetics are still being bandied about by certain race maniacs for the "improvement" of the human race or the breeding of a master race of *herrenvolk*. Thus it is often claimed, on their behalf, that since the poor breed faster than the rich, this differential birth rate will lead to the "degeneration" of the population. If their argument is correct, a society, in which men rose by their abilities and married a number of wives, while many of the poor remained unmarried, would inevitably enjoy a slow but steady increase in intelligence. And yet, this is not borne out by the only case, where we can perhaps point to a historical precedent. As J B.S. Haldane observed in his book *Heredity and Politics*, "For more than a thousand years the Mohammedans in Western Asia have practised polygamy, whilst Christians and Jews have not. Of course, only the richer Mohammedans could afford a harem. We should therefore expect that the Mohammedans would on the whole be superior to the Jews or Christians in intellectual qualities or at any rate in those qualities which make for the acquisition of wealth. In particular, a Turk should generally beat an Armenian or a Jew in a business deal. This is notoriously not the case. And, because it is not the case it is to be presumed that there is some fallacy in the arguments as to the trend of our national intelligence which are drawn from the study of differential birth rates". He considered that the whole basis of positive eugenics is far too flimsy to warrant any of the proposed measures to "improve" the level of intelligence in the population. We cannot as yet assess human intelligence properly let alone improve it. The diverse systems of intelligence quotients (IQ) devised by psychologists do not differentiate between the different "mental" factors involved therein. They simply measure, what one psychologist wrote, "conglomerates of heterogeneous abilities combined in unknown (and varying) proportions". As a result the intelligence tests claim to measure is simply "what the tests tested for", as E.G. Boring pointed out over 60 years ago. The consequential self-stultifying circularity of the tests is the main cause of the unhappy

confusion even among the testers themselves as to the meaning of the test. The main problem here is that they seek to measure something about which they seem to know as yet precious little. J.P. Guilford, for example, theoretically distinguished as many as 120 highly specific abilities through a cross-classification of cognitive (knowing) activities into logically discernible processes such as remembering, divergent thinking, etc.

In view of such a plethora of aspects of intelligence as the work of Guilford and others has recently revealed, it is futile to look for a satisfactory definition of intelligence. It is obviously too complex to be trapped even in a succint verbal net let alone a mere number devised by a tester. It is, therefore, even more hopeless to discover the genes that sponsor it. No wonder J.B S. Haldane despaired of discovering its genetical source. He held that if experience gained by animal genetical is any guide, "future work is likely to reveal entirely unsuspected facts concerning the determination of human intellectual capacity. The whole matter will only be cleared by very careful combined work by geneticists, biochemists, psychologists, and others, work which in its early stages will probably appear to be quite unnecessarily abstract and academic"

If one may hazard a guess, it will take a thousand years of intensive research before genetics can come of age to provide a truly scientific basis for the improvement of human intelligence. For the socially desirable qualities of human head and heart are so diverse and our ignorance of their genetical basis so great that there is no knowing yet how and where to begin such a eugenic programme. Even in academic circles, great achievement does not always go hand in hand with great intelligence, nor is great intelligence regularly transmissible to children. In a long-term study of the future careers of gifted young people, the results can be summarized by saying that the subjects married spouses of higher IQ than average but not as high as their own, and that their children had also a relatively high IQ but there was a wide scatter and only a small proportion could reach the intellectual level of the "index" parents. Admittedly there are some famous upper-

middle-class intellectual families in England like the famous Huxley's which have gone on producing highly distinguished men and women for generations. But how much of it was due to inheritance from both parents and how much due to the home, the educational environment, opportunity to excel, and the tradition of the class is as yet anyone's guess. Moreover, it must be emphasised that technical difficulties will prevent the genetic analysis in man of all characters except a few oligogenic traits, like the blood groups and the matabolic and some other genetic features. We have no adequate genetic analysis of a single polygenic trait in men, and one must assume that the characteristics that are particularly important to mankind the components of intelligence, character' and so forth are highly polygenic. As Haldane observed, if we want to breed a race of angels, we would have to obtain mutations, both for the wings and for the moral excellence. It, therefore, seems that eugenic proposals for such a wide-ranging project as the improvement of human intellect and character are extremely premature.

Unfortunately, our gross ignorance of the genetic basis of human intellect has not prevented the advocacy of certain *dysgenic* measures designed to eliminate from a population by compulsory sterilization detrimental genes responsible for serious genetical diseases and defects. Some states in U S.A. like California-have already begun to practice such preventive eugenics by enacting a law requiring sterilization of epilepties, of the insane, and of people who are hopeless cripples at birth even though we cannot be sure that these defects are always of genetic origin. Insanity is a case in point. In a life of extreme nervous stress a person of normal genotype might conceivably become insane like Hamlet or King Lear, and obviously sterilization of normals who had become insane would not prevent normals from becoming insane under similar circumstances.

Sterilization may seem at first sight a suitable measure for the elimination of such serious defects as are definitely known to be of genetic origin, as for example, amauratic idiocy, heamophilia, sickle cell anaemia, Huntington's Chorea, phenylketorunia, Tay Sach's disease, etc. But even here its efficacy

is severely limited. For it is only when a hereditary disease is directly caused by a single *dominant* gene like sickle cell anaemia or Huntington's Chorea that the defect could be wiped out within one generation if all persons affected by it were sterilized. But where the defect appears early in life and is so serious as completely to prevent reproduction as in sickle cell anaemia, nothing is gained by sterilization. In others, where the defect shows itself after the individual comes of age to reproduce or even later in middle life as in Huntington's Chorea, he may have begat all the children he intended to have. Sterilization then is like locking the stable door after the steed is stolen. There is thus little point in the artificial control of a dominant deterimental gene particularly as disabilities caused by such a gene are extremely rare. Natural selection itself is the most effective controller, if we do not interfere with it by devising elaborate and expensive cures to keep them alive and fit enough to breed the next generation as in heamophilia. It is true that there are other genetic diseases caused by recessive genes which are relatively much more frequent. But the individual is protected if he receives the dominant allele from the second parent. For the disease manifests itself only if he receives two recessive genes one from each parent. Sterilization of such defective or diseased individuals cannot effectively remove the guilty gene in a single or for that matter in several generations. It can be shown that a heterozygous population of genotype (Aa) where a is a recessive deterimental allele will have its gene frequency reduced from 50 to $33\frac{1}{3}$, to 25, to 20 per cent in the first four successive generations by sterilization of the defective genotype (aa) which alone will show the associated defect. As will be observed, the absolute amount of the decrease becomes less and less in each generation becoming still lesser in later generations. Thus in going from ninth to tenth generation the gene frequency would be reduced only from 10 to 9 per cent and it would take another 90 generations to reduce it to 1 per cent. But if the original population had initially a lower frequency of gene (a) say, only 10 per cent instead of 50 per cent of the above illustration, its elimination would take even longer. For the less its frequency in the original population the more difficult its

elimination by sterilization or selection. Now, the human race has a great many defective genes, but, for the most part, any *one* kind has a very low frequency. Consequently selection against any particular defective gene is an extremely slow process. No measure of sterilization would have any appreciable results in even ten generations by way of eliminating a rare (recessive) determental gene from the population even if there were no fresh input of similar genes by mutation.

If it takes extremely long to exorcise a rare deterimental gene from a population by selection or sterilization, the spread of a rare newly arisen mutant gene in a population takes *mutatis mutandi* equally long. This is why it is very difficult to properly assess genetic damage due to radiation hazard of nuclear explosions. Nuclear explosions result in the nearly instantaneous production of immense amounts of highly penetrating radiation and cause contamination by radiactive fallout of large areas. Within the area reached by direct ionizng radiation, great amounts of radioactivity are induced.

The dose of radiation received by an individual depends on his distance from the centre of the explosion. Most individuals who are near enough to receive a total radiation of about 450 roentgens[1] do not survive. But those who are further away are not entirely safe. For radioactive fallout following a nuclear explosion can cover with high concentration hundreds or thousands of square miles, in lower concentrations, the whole globe. It is, therefore, inevitable that radioactive fallout following nuclear explosions should give rise to mutations exactly as mutations may be induced artificially by exposure to X- rays, ultraviolet light and other sources of energy.

Such radiation-induced mutation may occur in two basically different anatomical regions: in body cells and germ cells. Body-cell or somatic mutations are not transmitted to later generations though they may damage the individual. But mutations in germ-cells or gametes are transmitted to the

[1] Roentgen is a unit measure of radiation which will produce ions carrying one electrostatic unit of electricity of either sign in one cc of dry air. It is measured by the amount of ionizations induced in a gas-filled chamber by the incident radiation in question.

offspring though they do not affect the exposed individual. Because the genetic damage caused by such mutations remains underground and cannot be distinguished from that caused by spontaneous mutations, its assessment has been grossly underestimated in the past by the apologists of political and other special interests Thus even a decade after the atomic bombings of Hiroshima and Nagasaki wide circulation was given to statements by certain prominent publicists, including physicians and others working on government projects, alleging that these bombings have left the populations unharmed or possibly even improved! Likewise, it was stated that the genetic damage caused in America by all the nuclear tests of both the super powers—the U.S.A. and the Soviet Union—was equal to that of a chest exposure to X-ray, about 0.1 roentgen. This amount is exceedingly minute and seems to suggest that the hazard caused by test explosions is negligible. But the fact that the genetic effects of radiation are cumulative both in space and time is seldom stressed. It is this fact that is the core of radiation hazard whether nuclear or otherwise A roentgen of radiation delivered in a low dose produces as much genetic damage as a roentgen delivered in a high dose. The greater the total amount of radiation, the greater the genetic damage. From a population standpoint, therefore, one roentgen dispensed among 1000 individuals produces as many genetic injuries as 10 roentgens delivered to 100 individuals, or 100 roentgens to 10 persons. Consequently the apparently insignificant exposure of 0.1 roentgen per person caused by the test explosions would aggregate in a population of 160 million to 16 million manroentgens. It is the same as that occurs when we expose a population of 160,000 persons to 100 roentgens. Assuming that the radiation dose received by Hiroshima survivors was adout 100 roentgens, the number of harmful mutations which will be inherited by the American in the future as a result of all test explosions turns out to be about the same as among the Japanese as a result of the Hiroshima atomic explosion.

This boomerang is the nemesis of the irrationality that led to the Hiroshima-Nagasaki atomic bombings. There is little doubt that *unlimited* nuclear testing is a serious genetic hazard

to future unborn generations. It is, therefore, folly not to ban the tests particularly as the porgress of science and technology for peaceful purposes alone is continually adding to the natural radiation load of man. For even if all nuclear tests were banned (a vain hope this), we must face the fact that man has inevitably to bear a certain amount of radiation exposure. Throughout the ages he has been exposed to what is called natural background radiation. It includes radiation from cosmic as well as terrestrial sources. Such radiation has probably played a major role in the evolution of life by providing mutations upon which natural selection has acted.

Since the discovery of radioactivity man has substantially added to his natural radiation burden. Medical X-rays are often necessary for the diagnosis or treatment of disease. In the affluent countries almost the entire population is exposed to periodic diagnostic X-rays and a significant fraction to therapeutic doses. Therapeutic doses vary widely depending upon, among other things, on the disease being treated. It may be as low as 0.1 roentgen as for chest X-ray or as high as 25 roentgens per examination in X-ray movie. High voltage power supplies for radar or television, X-ray machines in shoe stores, dental X-rays, luminous dial watches, and other products of super-consumer societies frequently give significant doses of radiation often much more than is warranted. A further significant contribution is made by nuclear power plants, a contribution that will increase enormously in future when more and more nuclear power plants are built to meet the energy crunch of our time. In consideration of the fact that the amount of radiation, exclusive of that from nuclear test explosions, to which man is exposed will increase in the future, several proposals have been made to limit the mean exposure of individuals in large populations to, at most, 10 roentgens per 30 years, a figure that sometimes includes natural background radiation and sometimes excludes it. Even this so-called permissible amount has far-reaching genetic consequences, particularly if the exposure occurs at a high level of intensity. It can be shown that such exposures will produce in each generation 20 per cent *more* genetically defective individuals than there were before the beginning of the

exposures. The time horizon for attaining this level, however, is different for different types of genes. With dominant genes, the increase to the new level will take only a few generations if the penetrance is high, more if it is low. For fully recessive genes the rise will be extremely gradual. But in course of time the new incidence of defetives, 20 per cent over the old, will eventually be attained. It, therefore, seems that long-range effects of the proposed limit are by no means insignificant. On the contrary, they are exceedingly grave. But because they will take many generations to surface, they will perhaps be ignored by the ruling elites of the world, who have a vested interest in the continuance of present trends, especially as we are still far below such deterimental exposures. Nevertheless, present trends cannot continue indefinitely. In due course, perhaps, a reduction of even this putatively permissible limit of 10 roentgens per thirty years may well become a categorical imperative.

## CHAPTER-XVI

# *Summing Up*

IN our exposition of modern genetics we have observed that life is essentially a pattern of self-sustaining chemical reactions. Their upshot is some building of a characteristic shape in almost all living things, a characteristic motion in most animals, feeling and purpose in some of them, and self-awarness in at least one of them. Although the chemical makeup of different living beings is very different—a tree is mostly wood which is not very like any of the constituents of a lamb—the chemical processes by which the roots grow into a tree and a lamb keeps itself alive are surprisingly similar. It is the similarity that makes them mutually complimentary. Thus animals consume foodstuffs while plants make them. But in both plants and animals the fundamental processes of building up and breaking down that are going on all the time are essentially alike. The reason for the basic sameness of life whatever its form whether a blue alga, an infusoria, an octopus or a human being is not far to seek. We know that all beings without exception are assemblages of cells. And recent advances in biochemistry, mainly during the second quarter of the present century, have revealed the profound and strict identity, on the microscopic level, of the functioning of the cell. We find that in all organisms from the bacterium to homo sapiens, the chemical machinery of

the cell is essentially the same in both its structure and functioning. Indeed, it could hardly be otherwise. For as we saw in Chapter-V, a cell is made mostly of proteins so that life is merely the mode of existence of proteins as Engels foresaw over a century ago. Since Engels wrote, the primary role of proteins in living processes has been further emphasised by the discovery that all these chemical reactions are catalysed by enzymes which are themselves proteins.

But enzymes and other proteins can be purified and will carry on their characteristic activities in a glass bottle. And no one can claim that such *in vitro* reactions make life. The chief feature of the pattern of chemical reactions that is life is its ability to beget a similar pattern. It does so by means of 'instruction's embodied in the genetic material, DNA, according to the genetic code that is universal in that the DNA→RNA protein system or some variant of it is operative in all living organisms. But the 'instructions' or information on the basis of which a new living being arises is always contained in the genome, the genes and chromosomes, of *another* structurally similar being, its parent(s).

Since the source of information of the ordered organisation of the organism is always another similarly ordered parental being, life is the emanation of order from order as was first envisaged by Schrodinger. Jaques Monod has called this ability of live organisms to transmit *ne virteur* the 'order' or rather information corresponding to their own structure "reproductive invariance". It is the property of reproductive invariance of live organisms that sets them apart from all other known objects in the universe with the sole exception of crystals. It is only the crystalline structures that are able to replicate themselves in a somewhat analogous way. But since crystalline structure represents a quantity of information, many orders of magnitude inferior to that transmitted from one generation to another even in the simplest organisms, living beings are a class of objects altogether different from all others including crystals. It is this dimensionally huge quantum of information that enables living beings not merely to breed their kind but also and—in this respect they differ

markedly from self-resproducing crystals—to grow and maintain themselves during all the diverse phases of their life.

Of these two distinctive properties of living beings namely, reproductive invariance on the one hand and self-growth as well as self-maintenance on the other, the latter seems more difficult to accomplish. Organic evolution took a giant stride in enabling organisms to perform it much more efficiently when it evolved beings equipped with a central nervous system. For there is, no doubt, that among all the multifarious perfections of this or that biological form to make it more fitted to survive nothing can compare with the pre-eminent role of the central nervous system that organises the whole animal and gives it a unity in its reaction to both its internal as well as external environment. Informed about its internal environment by a network of different neurons as well as by an intricate system of chemical messengers the harmones, it maintains the constancy of its *milieu interne* by issuing commands via different neurons and other glandular internal secretions. Likewise, it has sense organs to inform it about its external environment and muscles to carry out the appropriate response at its bidding. In short, such animals are self-growing, self-sustaining natural automata having a certain minimum quantity of information which confers on them the dual property of self-maintenance and reproductive invariance.

Now we can also make artificial automata like computers which operate on the basis of information embodied in their programme tapes. We should normally expect the yield or output of such an automaton to be a shade less complicated than itself. In particular, if an automaton has the ability to construct another, there must be a decrease in complication as we proceed from the parent to the progeny. For the parent must somehow contain within it not only a complete description of the offspring it breeds but also various arrangements to carry out the instructions to implement the description. In consequence, some decrease in complexity or 'patternedness' is to be expected as one automaton makes another. Nevertheless, the expectation is clearly contrary to the most obvious facts of life. Organisms not only reproduce themselves, that is, give birth to new ones with no decrease in complexity, but

have even produced during the long billennia of evolution increasingly complex beings. The English logician, A.M. Turing was the first to resolve this conflict between actuality and anticipation. He gave a logically rigorous rationale of all such duplicating processes whether natural or artificial. He showed that any automaton or computing machine that has the *minimum* proper information, or more precisely, the minimum proper number of instructions, can simulate any other automaton, however, large the instruction repertoire of the latter. In other words, there need be no dimunition in complexity as one automaton constructs another. On the other hand, it may well increase so that it may be made to reproduce another twice as effective and complex as itself.

While machines can be designed to utilize Turing's principle of one automaton reproducing another by reading its description from a tape, von Neumann has broadened the principle to cover the phenomenon of biological reproduction actually at work in nature. For the description may be recorded not merely on a paper tape or punch card but also in the genetic material (DNA) of which genes and chromosomes are made He has shown that on the basis of certain logically rigorous definitions of what constitutes an automaton, construction, reproduction, and so on, it is entirely feasible to reformulate Turing's principle in an extended context to yield a valuable insight into the nature of biological reproduction. His main conclusion is that while 'complication' on its lower levels is probably degenerative—that is, while every automaton that can produce another will be able to produce less complicated ones—once it exceeds a certain minimum critical level—the threshold level—it can and does evade this degenerative tendency. Degeneration of reproductive information is therefore like gravity in that, to escape it, the system must accumulate a certain minimum (threshold) of complication in one case and velocity in the other. Once arrived at this critical point, automata which can reproduce themselves or even construct higher entities become possible. This fact—that complication as well as organisation below a certain minimum level is degenerative but above it can become self-supporting or even increasing—is the basis of the emergence of life from

its inanimate roots. It is writ large in its subsequent evolution from its probable origin in some 'subvital' antocatalytic molecule of protein all the way to man.

Unfortunately, Turing-Neumann proof of the existence of a minimum threshold of information where 'complication' and organization cease to be degenerative and become self-amplifying is a piece of those beautiful existence theorems of pure mathematicians which prove that an entity exists without being able to produce it in flesh and blood. Although Turing-Neumann theorem does not yield the threshold minimum it otherwise guarantees, it is not an irremediable handicap. For we can substitute the deed, the living organism itself whose genome is the repository of information in excess of Neumann's threshold, for the demonstration. If we do so and consider a natural automaton like the living brain of a gorilla, we find that its storage capacity is of the order of $10^{14}$ bits[1] which is ten to hundred million times greater than that of the largest man-made computer. We need hardly be surprised at the vast gulf between the information capacity of natural and artificial atomata. For there is a fundamental difference between the living and natural automata such as animals with living brains like gorilla and artificial automata like computers. Thus while no computer is ever made merely to maintain itself -its primary function is to duplicate some special human skill like counting, computing, storing, playing Turing's well-known imitation game of holding its own in conversation with a human being—the sole purpose of the animal machine (that is, life) is, apart from reproduction, simply to keep on living.

But living is no simple matter even if animals seem to continue living effortlessly. It requires the automatic performance of myriad physiological functions of the body like maintaining blood sugar, bvdy temperature, or blood pressure at a particular level, or regulating breathing rate, or heart beat, or producing antibodies to counter microbial invasions as also gametes for reproduction, and many others which we have

* Bit is the unit in which information content of a message is measured. It is the number of dots and dashes required to transmit the message via morse code.

yet to discover and decipher. When we consider the great multitude of tasks that the living body has to perform merely to keep itself alive, let alone breed another of its kind. we do not really marvel that the minimum threshold information required to make it and then maintain it during the course of its life is so colossal. The real marvel is rather how this colossal information is locked in tiny DNA macromolecules, the genes. An equal marvel at first sight is nature's departure from her normal practice of prodigal provision. Ordinarily to provide for one oak she produces a myriad acorns, for a single baby a million sperms, for a lone life an exploding population, for a solitary bush a bush forest. But for writing the secret of life she seems to have departed from this norm and devised only one code, the universal genetic code described in Chapter V, when myriads of similar codes could have served as well. If nature ever tried another gentic code (s) we have no evidence thereof. There is perhaps a very good reason for nature's parsimony in making genetic codes. A plethora of codes would not have permitted the mutual interdependence of life and thwarted even the microevolution of life. This is also why, of the two isomeric forms of amino acids—the so-called L and D amino acids which are mirror images of each other—it is only L types that actually occur in proteins. Because the genetic code is universal and the amino acids in proteins are all of one (L) type there prevails the virtual identity of cellular chemistry[1] throughout the biosphere. It accounts for the fact already noted that chemical machinery of the cell is essentially the same both in its structure and its functioning.

Consider first cell structure. All living beings, without exception, are made up of the same two principal classes of macromolecules—proteins and nucleic acids. More importantly, these macromolecules are made up in all living beings by the assembly of the same residues, twenty L-type amino

[1] Another type of cellular chemistry based on a different genetic code and D-type amino acids might exist on other planetary worlds in our galaxy or other galaxies. But we have as yet no knowledge of them.

acids for the proteins and for nucleotides four nucleic acids. As for its functioning, the same reactions or rather sequences of reactions we earlier called metabolic pathways are used in all organisms for the essential chemical operations, namely, the mobilization and storing of chemical potential, and the biosynthesis of cellular components. It is, no doubt, true that this central theme of metabolism has many variations each corresponding to a particular functional adaptation. But they almost always consist in minor departures from universal metabolic sequences. For example, the birds and mammals excrete nitrogen in different ways; the former excrete uric acid, the latter urea. But the pathway for the synthesis of uric acid in birds is only a minor modification of the sequence of reactions which in all organisms synthesizes the so-called purine nucleotides, the universal components of nucleic acid. Likewise, the mammalian synthesis of urea is a modification of another universal metabolic pathway which concludes with the synthesis of the amino acid arginine present in all proteins. Such examples of universal metabolic pathways could be multiplied ad lib.

The existence of universal forms of metabolic pathways, the heart of cellular chemistry, is no mere accident. It stems from the existence of universal components : the nucleotides of nucleic acids on the one hand and amino acids of proteins on the other. They are the logical equivalents of an alphabet in which the structure and consequently the associative functions of proteins are spelt out. In this alphabet, can therefore be written all the diversity of structures and performances the bioshpere contains. Moreover, with each succeeding cellular generation it is the *hi fi* reproduction of the text, written in the form of DNA nucleotides sequences, that guarantees the reproductive invariance of the species as we have already seen.

However, the *hi fi* reproduction is not absolute because of the operation of quantum mechanical laws. These laws stipulate that save at absolute zero, an inaccessible limit, no microscopic entity can fail to undergo quantum perturbations whose accumulation within a macroscopic system will slowly but inevitably alter its structure. It is, therefore, no wonder

that living beings, despite the perfection of the reproductive machinery that guarantees the *hi fi* translation of genetic information, are not exempt from this law. Some of these quantum perturbations do create more or less discrete modifications in certain elements of the DNA sequence. Another source of these perturbations is exposure to radiation both natural as well as man made. Such errors of replication, called mutations, thanks to the unfailing fidelity of the reproductive mechanism, are automatically replicated with the consequences we have already described. The most important of them is that mutational disturbance of reproductive invariance is the main spur that has directed biological evolution under diverse selection pressures generated by changing environment. For even though in living beings these random mutational perturbations are mostly injurious, yet once in a rare while they do give rise to a new organism better able to adapt itself to its changing environment than its parental forms. It is precisely these beneficial though rare mutational perturbations, the stray stirrings of the genome, snapped and reproduced by the replicative mechanism, that have been retained by natural selection and have led first to the irruption of life from its inanimate beginnings and then to its blossoming into those myriad forms which starting from some subvital autocatalytic macromolecule of protein have culminated in man. Consequently, as Jacques Monod has observed, "*evolution is not a property of living beings* since it stems from the very *imperfections* of the conservative (reproductive) mechanism which indeed constitutes their unique privilege. And so one may say that the same source of fortuitous perturbations, of 'noise', which in a non-living (non-replicative) system would lead little by little to the disintegration of a structure is the progenitor of evolution in the biosphere and accounts for its unrestricted liberty of creation, thanks to the replicative structure of DNA: that registry of chance, that tone-deaf conservatory where the noise is preserved along with the music". However, Monod's observation is apt to mislead because he omits to mention the discriminatory mechanism at work that suppresses all unwanted "noise" and conserves only that small fraction of it

which happens to be in tune with the "music" of evolution. For if DNA, the repository of all chance mutations is tone-deaf, natural selection that conducts this "music" is *not*, It is natural selection that decides which mutation or "noise" is to be preserved and which suppressed depending on its survival value to the organism in the ambient environment in which it lives.

Modern theory of evolution is thus a reversal of the earlier Lamarckian dogma that regarded evolution as an innate property of living beings. For it held that organisms do respond to environmental changes calling forth new needs by new adaptations which are heritables. And evolution proceeds by the transmission of such heritable adaptations. However, adaptations are of two types according as they pertain to physical traits like eye colour, skin complexion, blood group, etc. or to modes of behaviour like speaking, erect walking etc. While physical traits of animals are the outcome of heredity and any such traits acquired after birth are not transmitted, the question whether their behaviour patterns are the result of heredity alone independent of neonetal environment is open. It seems that animals lower down the evolutionary ladder like bees and birds are born with their behaviourial patterns like the courting dances of the former and navigational instincts of the latter genetically fixed once for all. But in the case of animals higher up the evolutionary scale neonatal experience plays an important role in determining their behaviourial pattern. This is the case even with some of the species of invertebrates such as the octupus. Although initially the functioning of their nervous system would be dependent solely on the inborn genetic inheritance they can be readily trained or conditioned so that the reaction of an individual comes to be a product not only of its genetic patrimony but also of the experiential encounters during its lifetime. There is evidence that even much simpler organisms such as worms have this faculty. However, it is with higher vertebrates that neonatal experience plays an increasingly significant role in determining the final shape of the living brain, in particular, the inter-connections of the neuronal network that is their central nervous system.

Take, for instance, man whose brain confers on him alone of all terrestrial creatures the strange faculty of speech and language. Recent work on cerebral mechanisms of human speech by neurophysiologist like Penfield, Roberts and others has shown that although man's brain in outward form is not so very different from that of other mammals like the dog, monkey, or gorilla, there is, within it a further sophistication of cerebral organization that makes human speech possible. But to actualize this potential of human brain environment plays a very considerable role. Anatomical evidence seems to show that the primary acquisition of language by the new born infant, is bound up with a process of embryological development. This development apparently consists not so much in the growth of neurone whose number ($10^{13}$) remains the same at birth as in adult brain but in a considerable amplification of the network of inter-connections between cortical neurons. Very rapid during the first two years, the process afterwords slows down, till it halts at puberty. It is significant that the period during which the cortical interconnections grow coincides with the critical period during which the infant acquires the gift of speech. If the new born infant is brought up in a jungle environment where human speech is not spoken, he remains for life dumb and mute. There are several well authenticated accounts of such babies deserted in the woods who were "adopted" by a bear or a wolf and were discovered after several years. For example, the "wild boy" Peter was found near Hanover in 1723, another Victor, the "savage of Aveyron" in Southern France in 1799, and Amala and Kamla in Midnapore, India, in 1920, not to mention the brood of new born babes Emperor Akbar is said to have brought up in seclusion without letting them hear any language in order to test if language is inborn or acquired. None of them spoke any language. One must, therefore, conclude that an embrological or epigenetic process occurs in the course of which the neural interconnections that enable linguistic performance develop. If during the critical period of this development the environment provides no opportunity for the practice of language, the individual never acquires the gift of speech. He

remains a sort of speechless humanoid.

Now it is language alone that sets man apart from all other living beings because it opens up to him alone and no other animal the limitless possibilities of using word symbols for things and so keeping them in mind when out of sight. It is the foundation on which are based more and more sophisticated usages of language in higher levels of symbolic and abstract thought. Without it there cannot exist man's unique achievement, the creation of what Karl Popper has called the third World (World$_3$) of objective knowledge as distinct from World$_1$ of physical objects and states and World$_2$ of subjective knowledge or states of consciousness. It is thus obvious that while genes are the main repository of information that has led to the unique cerebral endowment of man, its characteristic performance, the actual practice of language and speech, occurs only if he grows up in an environment where a language is spoken by his tribe. This is why man's further evolution since his emergence has proceeded *not* by the growth of information in his genes but in the environmental matrix of his creation, the World$_3$ of objective knowledge. Since the precise cortical organisation of human cerebral cortex that enables him first to learn to speak and thus armed to familiarize himself with World$_2$ of objective knowledge depends greatly on appropriate neonatal environment, the old debate about the relative contributions of heredity (genes) and environment (nurture) in making the *mind* of man is by no means closed. The debate harks back to Aristotle who saw the human brain as *tabala rasa* on which the experience merely recorded itself like pictures etched on waxwork or writing on sand. Later philosophers like Locke, Polyneus and Berkley believed that in order to perceive the world, the eyes (and the brain) must first experience it. Nurture they thought is important. From what we have observed, it seems that these philosophers were substantially right. For although man is genetically equipped with the potentiality of speech, he cannot utter a single word by instinct. His inborn faculty of speech remains, in the absence of a lingual environment, dormant forever.

The evolution of man with his dormant genetic gift of speech

that requires a special environment to wake it up from its deep slumber is an evolutionary discontinuity or singularity as epochal as the origin of life itself. Dobzahsky has called both these events—the origin of life and origin of man—"transcendences" in the continum of biological evolution. As he has remarked, "human mind did not arise from some kind of rudimentary minds of molecules and atoms. Evolution is not simply unpacking of what was there in a hidden state from the beginning. It is a source of novelty, forms of being which did not occur at all in the ancestral states".

Just as the origin of the first living organism transcended the simple physical and chemical properties of its elementary constituents and involved a degree of complication or accumulation of "order" decidedly different in kind from that involved in the inorganic synthesis of the most complicated macromolecule, so also the origin of man represents the creation of a new being that is now able to direct his own evolution by the accumulation of its acquired heritage, the World$_3$ of objective knowledge. It is able to do so because the human brain has evolved a surplus cerebral capacity that is not tied wholly to the performance of the dual tasks of all other live organisms—self-maintenance and reproductive invariance. It has been estimated that while the cerebral capacity of gorilla brain is $10^{14}$ bits that of the human brain is $10^{15}$ bits. Assuming that $10^{14}$ bits is the minimum threshold of information required for self-maintenance and reproduction of an organisation as complex as a gorilla or man there is in man a vast reservoir $(10^{15} - 10^{14}) = 9 \times 10^{14}$ bits of cerebral power available for his practice of language, science, technology and other cultural pursuits. It thus happens that while only ten per cent of his cerebral capacity suffices to perform all the physiological functions of his animal existence the remainder 90 per cent enables him to become what he is, namely, Homo sapien, man the wise.

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